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SPLENECTOMY FOR MYELOID METAPLASIA OF THE SPLEEN*

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SINCE the report of Rathery[1] in 1902, many cases of leukoerythroblastic anemia associated with myelofibrosis and myeloid metaplasia of the spleen have been described. This syndrome has been designated by a variety of descriptive terms, among which "agnogenic myeloid metaplasia"[2] has been popular in recent years. The subject has been extensively reviewed by several authors.[3-5] Donhauser,[6] in 1908, suggested that the disorder was brought about by a primary depression of bone-marrow function, possibly resulting from toxic or other untoward influences, and that extramedullary blood formation occurred in the spleen and liver as a compensatory reaction. In 1937 Hickling[3] first called attention to the high mortality after splenectomy in this syndrome. More recently Jackson, Parker and Lemon[2] have warned against splenectomy or splenic irradiation. There is now a widespread belief that removal or irradiation of the spleen destroys an important area of blood formation, and that the procedure will lead to harmful if not fatal results. Myeloid metaplasia of the spleen is generally considered to be the outstanding contraindication to splenectomy,[7, 8] which has nevertheless been performed in many cases of "agnogenic myeloid metaplasia." Bukh and With,[9] in 1945, collected 54 cases of this disorder in which splenectomy had been performed, and numerous other cases have been reported. A careful review of the individual case histories provides no support for the concept that the harmful results of splenectomy can be attributed to removal of a large area of blood-forming tissue. On the other hand, an occasional patient has shown definite clinical and hematologic improvement after the operation.

We have had the opportunity to study 5 patients with "agnogenic myeloid metaplasia" who were subjected to splenectomy. In no case was there any apparent deleterious effect, and 1 patient was obviously improved. Four of these patients were demonstrated to have myelofibrosis, and all had a leukoerythroblastic peripheral blood pattern and myeloid metaplasia in the spleen or liver. Splenomegaly had been a prominent feature of each case before splenectomy. Four of the 5 patients have been under observation for more than four years since the spleen was removed.

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CASE REPORTS

CASE 1. E. D. (J.H.H. 314923), an awning maker, was admitted to the hospital on five occasions between 1927 and 1950 and was 46 years old at the time of his last admission. He was said to have contracted malaria in Nicaragua in 1923. In 1927 he was admitted to the hospital with a history of recurrent chills and fever for 10 days, and at that time the edge of the spleen was palpable. The hemoglobin was recorded as 88 per cent, and the white-cell count as 9100, with a normal differential count. No malarial parasites could be demonstrated in blood smears, but the symptoms subsided during therapy with quinine. In 1931, when he was readmitted for herniorrhaphy, the spleen was again felt, the hemoglobin was 95 per cent, and the white-cell count 7000. He re-entered the hospital in February, 1944, because of pain in the back and legs associated with intermittent chills, fever and malaise of 11 weeks' duration. The temperature was normal on admission, but the tip of the spleen was palpable. The hematocrit was 48 per cent, and the white-cell count 7100, with a normal differential count. No malarial parasites were seen in the blood smears. The cause of the symptoms was not identified, but they were temporarily controlled by the administration of aspirin. In September, 1945, he was admitted to another hospital because of recurrence of his symptoms, together with weakness and purpura of several weeks' duration. The spleen was greatly enlarged.

Examination of the blood showed a red-cell count of 2,700,000 with a hemoglobin of 7.4 gm. per 100 cc., and a white-cell count of 1950, with 60 per cent neutrophils, 16 per cent lymphocytes, 12 per cent monocytes, 8 per cent eosinophils and 4 per cent basophils. Platelets were reduced to 38,000. The reticulocyte count was 1.9 per cent. The clotting time was 6 minutes, and the bleeding time 30 minutes. He was considered to have Banti's syndrome, and splenectomy was performed.

The spleen weighed 1500 gm., and sections, sent to the Johns Hopkins Hospital for examination, showed the typical features of myeloid metaplasia, with islands of blood-forming cells scattered throughout the splenic pulp (Fig. 1). Convalescence was uneventful. The marked bleeding tendency ceased immediately after the operation, and the platelet count was 87,000 on the 2d postoperative day.

He remained well until four months before his fourth admission to the Johns Hopkins Hospital in May, 1947, when the aching pain in the legs, chills, fever and increasing weak-

ness recurred. On questioning, no history of exposure to benzene or other known bone-marrow toxins could be obtained. The temperature was 102°F. by rectum, the pulse 88, and the respirations 20; the blood pressure was 130/80. He appeared chronically ill without evidence of weight loss. The liver edge was palpated at the costal margin, and the splenectomy scar was well healed. The red-cell count was 2,960,000, with a hemoglobin of 9.3 gm. per 100 cc., hematocrit of 30.6 per cent, mean corpuscular volume of 103 cubic microns, mean corpuscular hemoglobin of 28 microgm., mean corpuscular hemoglobin concentration of 27 per cent and icteric index of 9 units. The white-cell count was 14,800, with 3 per cent myelocytes, 11.5 per cent juvenile and 31.5 per cent mature neutrophils, 4 per cent juvenile and 9 per cent mature eosinophils, 2.5 per cent basophils, 36.5 per cent lymphocytes and 2 per cent monocytes. The nucleated red-cell count was 8700, and the platelet count 450,000. The bleeding time was 2 minutes, and the clotting time 9 minutes. An osmotic fragility test showed beginning hemolysis at 0.54 per cent sodium chloride solution and complete hemolysis at 0.21 per cent (control, 0.48 and 0.33 per cent). On the blood smear the red cells showed a remarkable degree of anisocytosis and poikilocytosis, moderate polychromatophilia and occasional stippling. Some giant and abnormal platelets were seen.

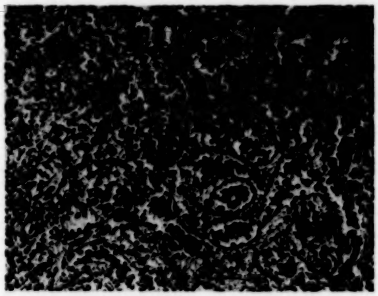

FIGURE 1. *Section of the Spleen in Case 1, Showing Myeloid Metaplasia (X150).*

The blood nonprotein nitrogen was 41 mg., the sugar 86 mg., the serum bilirubin 1.4 mg., the calcium 9.7 mg. and the phosphorus 5.1 mg. per 100 cc., and the alkaline phosphatase 2.9 Bodansky units; the albumin was 4.3 gm. and the globulin 1.7 gm. per 100 cc. Roentgenograms of the chest and skull were normal. A biopsy of the sternum was performed, and the sections showed fibrosis of the bone marrow, with an increased proportion of nucleated red cells. The hematocrit rose to 40 per cent after the administration of 2500 cc. of whole blood.

No other transfusions were given during the next 2 years. The patient was frequently observed in the outpatient department, and except for mild aching discomfort in the legs was remarkably well. During this period the hematocrit varied between 27 and 46 per cent. The white-cell count was persistently elevated, ranging between 14,000 and 34,000. Myeloblasts were usually seen in the blood smears, at times reaching 15 per cent. Myelocytes were always present. Nucleated red cells were extremely numerous, ranging from 14 to 207 per 100 white cells. Bone marrow aspirated from the sternum in 1949 was cellular and showed a great preponderance of erythroid elements, some of which closely resembled megaloblasts. The red cells were persistently macrocytic and showed marked anisocytosis and poikilocytosis, with polychromatophilia, target cells and Howell—Jolly bodies. The platelet count was elevated to 670,000, more than twice the normal value. Roentgenograms of the pelvis and long bones in 1949 showed no abnormality.

The patient was readmitted to the hospital in June, 1949, because of increasing weakness, dyspnea and fatigue. There was moderate pallor but no jaundice. The liver edge was palpable 7 cm. below the costal margin. At this time the hematocrit was 30 per cent, the white-cell count 21,000, and the nucleated red-cell count 20,400. The concentration of urobilinogen in the feces was within normal limits. A biopsy of the left ilium was performed. The sections showed myelofibrosis,

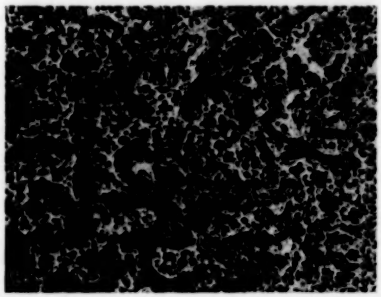

FIGURE 2. *Section of the Liver in Case 1, Showing Myeloid Metaplasia (X150).*

with areas of myeloid and erythroid hyperplasia. The administration of folic acid and vitamin B_{12} had no detectable effect. He was given a transfusion of 1500 cc. of blood.

He remained in fairly good health until several weeks before his final admission in April, 1950, when typical symptoms of peptic ulcer developed. The hematocrit, which had stabi-

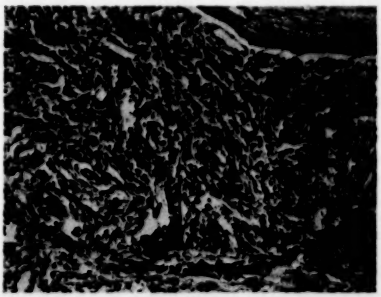

FIGURE 3. *Section of the Bone Marrow in Case 1, Showing Fibrosis (X150).*

lized at about 37 per cent, dropped abruptly after the passage of several tarry stools. X-ray studies were interpreted as showing a prepyloric ulcer, possibly malignant, and for this reason an exploratory laparotomy was performed. He was found to have a benign ulceration of the duodenum, and a subtotal gastrectomy was performed. After the operation, there was persistent bleeding into the peritoneal cavity. On re-exploration, no cause for the abnormal bleeding could be

found. Although many transfusions were given, he died in shock on the 1st postoperative day.

At autopsy bone marrow obtained from several sites was fibrotic, with foci of myeloid hyperplasia. The liver weighed

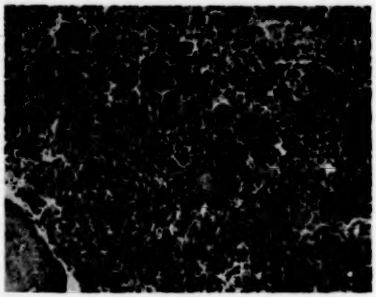

FIGURE 4. *Further Sections of the Bone Marrow in Case 1, Showing Myeloid and Megakaryocytic Hyperplasia (X150).*

3250 gm. and contained numerous areas of myeloid metaplasia. Sections of the liver and bone marrow are shown in Figures 2–4. Some of the lymph nodes also showed myeloid metaplasia, but there were no changes suggestive of leukemia.

CASE 2. J. G. (J.H.H. 475174), a 41-year-old coal miner, was admitted to the hospital in October, 1948, because of vague discomfort in the right upper quadrant of the abdomen. In June, 1947, he had been examined at another hospital for similar symptoms. At that time he was found to have a large spleen; the white-cell count was said to be 12,000, with a normal differential count, and the hemoglobin 82 per cent. Splenectomy was performed, the spleen weighing approximately 1500 gm. Thereafter, he remained well until 9 months before admission, when the right-upper-quadrant discomfort recurred and he noted the presence of a mass in the right side of the abdomen. There was no history of exposure to benzene or other known toxic agents. The temperature was 99.0°F. by rectum, the pulse 90, and the respirations 18; the blood pressure was 130/70. The patient appeared well, without evidence of acute or chronic illness. There was no palpable lymph-node enlargement. The liver edge was felt 3 cm. below the costal margin, and the splenectomy wound was well healed. The red-cell count was 5,700,000, the hemoglobin 15 gm. per 100 cc., the hematocrit 47 per cent, the mean corpuscular volume 82 cubic microns, the mean corpuscular hemoglobin 26 microgm., the mean corpuscular hemoglobin concentration 32 per cent, and the icteric index 7.5 units. The white-cell count was 35,900, with 0.5 per cent myeloblasts, 0.5 per cent myelocytes, 6.5 per cent juvenile and 54.5 per cent mature neutrophils, 4.5 per cent eosinophils, 1.0 per cent basophils, 21.5 per cent lymphocytes and 11 per cent monocytes. There were 4.2 per cent reticulocytes and 1 nucleated red cell per 100 white cells. The platelet count was 1,490,000, the bleeding time 2 minutes, and the clotting time 9 minutes. Clot retraction was normal, and the tourniquet test negative. An osmotic fragility test showed beginning hemolysis in 0.54 per cent sodium chloride solution and complete hemolysis at 0.27 per cent (control, 0.45 and 0.30 per cent). On the blood smears the red cells showed slight anisocytosis, poikilocytosis and rare polychromatophilia. The blood nonprotein nitrogen was 46 mg., and the sugar 94 mg. per 100 cc. The serum bilirubin was less than 0.8 mg. per 100 cc. The cephalin-flocculation test was negative, and the thymol turbidity 4.2 units; the prothrombin time was normal. The alkaline phosphatase was 5.2 Bodansky units, and the uric acid 5.5 mg. per 100 cc. Free hydrochloric acid was present in the gastric secretion. X-ray films of the chest and long bones showed no abnormality. Biopsy of the sternum was performed, the sections showing myelofibrosis with areas of myeloid and megakaryocytic hyperplasia (Fig. 5). The sections of the spleen, which were reviewed, demonstrated myeloid metaplasia.

The patient returned to the hospital in April, 1949, for re-evaluation of his disease. His symptoms were unchanged, and his general health was good. The physical status and results of laboratory tests were virtually the same as on the 1st admission. A small lymph node was removed and on section showed myeloid hyperplasia, resembling that seen in leukemia. However, biopsy of a rib showed only osteosclerosis and myelofibrosis.

He was readmitted to the hospital for examination in October, 1951, more than 4 years after the splenectomy had been performed. At that time he complained of moderate weakness, fatigability, headaches and occasional epistaxes. Physical signs were unchanged except that the liver edge extended 7 cm. below the costal margin. The red-cell count was 5,300,000, the hemoglobin 15 gm., the hematocrit 45 per cent, the mean corpuscular volume 85 cubic microns, the mean corpuscular hemoglobin 28 microgm., and the mean corpuscular hemoglobin concentration 33 per cent. The white-cell count

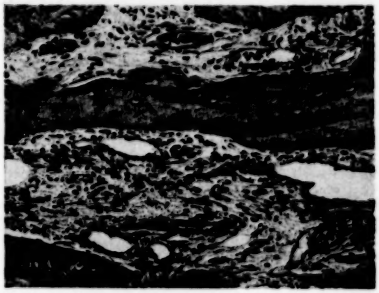

FIGURE 5. *Section of the Bone Marrow in Case 2, Showing Osteosclerosis and Myelofibrosis (X150).*

was 30,400, with 8 per cent myelocytes, 8 per cent juvenile and 57.5 per cent mature neutrophils, 1.5 per cent eosinophils, 0.5 per cent basophils, 17.5 per cent lymphocytes and 7.0 per cent monocytes. The platelet count was 1,580,000. There were 2.2 per cent reticulocytes and 3 nucleated red cells per 100 white cells. The nonprotein nitrogen was 27 mg. per 100 cc. of blood, alkaline phosphatase 5.9 Bodansky units, cephalin flocculation +, and thymol turbidity 11.5 units; the serum albumin was 4.6 gm., the globulin 2.5 gm., the uric acid 6.3 mg., and the bilirubin less than 0.8 mg. per 100 cc. There was no retention of bromsulfalein, and the prothrombin time was normal. Attempts to aspirate bone marrow on 4 occasions between 1948 and 1951 were unsuccessful, presumably because of the myelofibrosis.

CASE 3. J. C. (U.S.P.H.S.H. 93062), a 64-year-old male laboratory worker, was admitted to the United States Public Health Service Hospital in Baltimore for investigation of a pulmonary lesion discovered on a routine roentgenogram. Twenty years before, splenectomy had been performed at another hospital because of splenomegaly. The spleen weighed 900 gm., but unfortunately the specimen and sections were lost in the ensuing years. For several years before admission the patient had had recurrent attacks of acute arthritis, without residual deformity. He had had a slight cough for several months, but otherwise was asymptomatic. There was no history of exposure to benzene or other toxic chemicals. The temperature was 98.6°F. by mouth, the pulse 88, and the respirations 20; the blood pressure was 104/60. He appeared

chronically ill, with some evidence of weight loss, and there was pallor of the skin and mucous membranes. The peripheral lymph nodes were not enlarged. The liver edge was palpable 10 cm. below the costal margin. The red-cell count was 2,780,000, the hemoglobin 9.7 gm. per 100 cc., the hematocrit 24 per cent, the mean corpuscular volume 86 cubic microns, the mean corpuscular hemoglobin 35 microgm., and the mean corpuscular hemoglobin concentration 40 per cent.

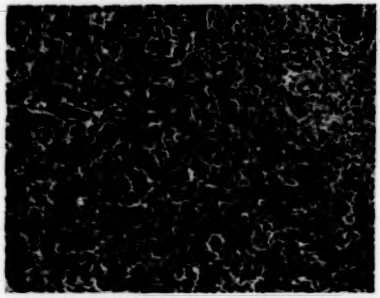

FIGURE 6. *Section of the Liver in Case 3, Showing Myeloid Metaplasia (X150).*

The white-cell count was 21,700, with 2 per cent myelocytes, 11 per cent juvenile and 67 per cent mature neutrophils and 20 per cent lymphocytes. There were 6 nucleated red cells per 100 white cells. The platelet count was 300,000, the bleeding time 1 minute, and the clotting time 4 minutes. Blood smears showed marked anisocytosis, poikilocytosis and polychromatophilia of the red cells, and there were many large

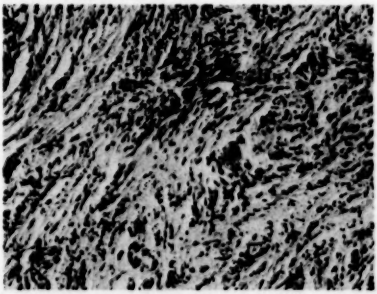

FIGURE 7. *Section of the Bone Marrow in Case 3, Showing Myelofibrosis (X150).*

and bizarre platelets. Urinalysis was negative except for numerous hyaline and granular casts and a few white cells in the sediment. The serum bilirubin was 0.4 mg., the albumin 3.9 gm., the globulin 3.4 gm., and the uric acid 2.9 mg. per 100 cc.; the thymol turbidity was 1.5 units, the alkaline phosphatase 4.3 Bodansky units, and the prothrombin 56 per cent of normal. There was no retention of bromsulfalein. Examination of the sputum was negative for tubercle bacilli. X-ray films of the chest disclosed a soft infiltration in the region of the 2d right interspace. Miliary calcifications were seen in the left upper lobe, and large calcifications in both hilar areas. Roentgenograms of the pelvis showed general coarsening of the bony trabeculae, but the skull and long bones appeared normal. Two attempts to aspirate bone marrow from the sternum were unsuccessful. Bone-marrow biopsies were obtained from several sites, the sections demonstrating myelofibrosis and megakaryocytic hyperplasia. Extensive areas of myeloid metaplasia were revealed in a liver biopsy. While in the hospital the patient suddenly gave evidence of a cerebrovascular accident and died soon thereafter.

At autopsy the liver weighed 1350 gm. and contained numerous foci of myeloid metaplasia (Fig. 6). Some of the

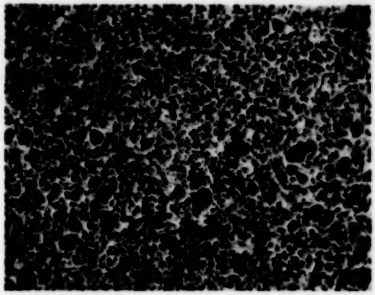

FIGURE 8. *Further Section of the Bone Marrow in Case 3 Showing Myeloid and Megakaryocytic Hyperplasia (X150).*

lymph nodes also contained areas of extramedullary blood formation. Sections of bone marrow in some areas disclosed osteosclerosis and myelofibrosis (Fig. 7), and in other areas myeloid and megakaryocytic hyperplasia was evident (Fig. 8). There was chronic active pulmonary tuberculosis. A recent thrombus occluded the right middle cerebral artery.

CASE 4. W. K. (M.H. 12939), a 61-year-old male cleric, had been admitted to the Mercy Hospital on many occasions since 1929, most often for transient gastrointestinal disturbances. On numerous physical examinations prior to 1944 no enlargement of the spleen or liver was observed. Many blood examinations had given normal results, including red-cell counts, hemoglobin determinations and white-cell and differential counts. There was no history of exposure to benzene or other myelotoxic agents. In 1944 the patient was readmitted to the hospital because of an episode of nausea and vomiting. The temperature was 98.4°F. by mouth, the pulse 80, and the respirations 18. The blood pressure was 120/80. He did not appear chronically ill, and there was no pallor or icterus. The liver edge was palpable 3 cm. below the costal margin, and the spleen filled most of the left upper quadrant, extending to the level of the umbilicus. There was no peripheral lymph-node enlargement. The red-cell count was 3,960,000, the hemoglobin 12.6 gm. per 100 cc., the hematocrit 39.0 per cent, the mean corpuscular volume 98 cubic microns, the mean corpuscular hemoglobin 32 microgm., and the mean corpuscular hemoglobin concentration 33 per cent. The white-cell count was 2750, with 18 per cent juvenile and 44 per cent mature neutrophils, 34 per cent lymphocytes and 4 per cent monocytes. There were 2 nucleated red cells per 100 white cells. The red cells displayed anisocytosis, poikilocytosis and polychromatophilia. An osmotic fragility test gave normal results. The cephalin-flocculation test was ++++. The patient was considered to have Banti's syndrome and was discharged without specific therapy.

Thereafter he was admitted at approximately monthly intervals for examination. The red-cell count varied between 3,800,000 and 4,500,000, the hemoglobin between 12.0 and 14.1 gm. per 100 cc., and the white-cell count between 3400 and 8800. The differential count was unchanged. One platelet count was recorded as 540,000 (indirect method). The blood sugar was 96 mg., the serum bilirubin 0.6 mg., the albumin 3.4 gm. and the globulin 2.1 gm. per 100 cc. Bromsulfalein retention after 45 minutes was 2.5 per cent.

At splenectomy, performed in April, 1945, the spleen measured 20 by 18 by 8 cm., but the weight was not recorded. On section, many foci of myeloid metaplasia were seen. Convalescence from the operation was uneventful. There was no tendency for the hemoglobin concentration to fall, and the white-cell count rose to over 10,000. There was a striking rise in the platelet count from the preoperative value to over 6,000,000 1 month later. The patient's general health was good at the time of discharge from the hospital.

During the next 3 years he returned on several occasions because of troublesome bleeding from the gums. At these times the platelet count ranged between 3,000,000 and 5,000,000, the prothrombin time was prolonged to 26 seconds (about 50 per cent of normal), and the bleeding time, clotting time, clot retraction and capillary fragility were normal. In December, 1945, he had an episode of gastrointestinal hemorrhage, after which the hemoglobin dropped to 5.6 gm. per 100 cc. No evidence of peptic ulcer, varices or other lesions could be demonstrated on roentgenographic examination. The patient improved after the administration of several blood transfusions. In October, 1946, he again became anemic after an episode of severe bleeding from the gums; he was given a transfusion at that time. About 3½ months later nausea, anorexia, epigastric discomfort, clay-colored stools, dark urine and jaundice developed. The liver was tender, and liver-function tests were transiently positive. This episode subsided within 2 months. Thereafter, liver-function tests were negative except for a cephalin flocculation graded as + and a prothrombin time ranging between 19 and 26 seconds.

In August, 1947, the patient was seen at another hospital where a bone-marrow biopsy was performed, sections showing cellular areas of myelopoiesis, with numerous megakaryocytes, and other areas of dense fibrosis. On examination in 1950 the patient was asymptomatic. At that time the red-cell count was 4,290,000, the hemoglobin 12.3 gm. per 100 cc., the hematocrit 40 per cent, and the platelet count 2,090,000. The white-cell count was 11,700, with 71 per cent neutrophils and 29 per cent lymphocytes. When last seen in May, 1952, he was very active and remarkably well. The hemoglobin was 13.3 gm. per 100 cc., and the platelet count 1,970,000.

Case 5. F. H. (J.H.H. 607185), a 52-year-old executive, was admitted to the hospital in May, 1952, because of weakness and night sweats. In 1948 laparotomy had been performed at another hospital for closure of a perforated peptic ulcer. Since that procedure he had been virtually asymptomatic on conventional ulcer therapy. Fourteen months before admission exertional dyspnea, fatigue and bleeding from the gums developed. The hemoglobin was said to be 77 per cent, and symptomatic improvement followed therapy with iron preparations. Three months before admission he experienced increasing fatigue, exertional dyspnea and anorexia. Two months later he noticed that he had become pale and that a large mass was present in the left upper quadrant of the abdomen. He became aware of fever and night sweats at about this time. There was no history of exposure to benzene or other bone-marrow toxins.

The temperature was 101.2°F. by mouth, and the pulse 100; the blood pressure was 106/42.

The patient appeared acutely ill, and there was a marked yellowish pallor. There was no peripheral lymph-node enlargement. The spleen filled most of the left upper quadrant, extending 16 cm. below the costal margin. The liver edge was palpated 5 cm. below the costal margin. The red-cell count was 2,940,000, the hemoglobin 7.9 gm. per 100 cc., the hematocrit 27 per cent, the mean corpuscular volume 92 cubic microns, the mean corpuscular hemoglobin 27 microgm., and the mean corpuscular hemoglobin concentration 29 per cent. The white-cell count was 2900, with 12 per cent myelocytes, 31 per cent juvenile and 26 per cent mature neutrophils, 2 per cent basophils, 13 per cent lymphocytes and 16 per cent monocytes. There were 2.3 per cent reticulocytes and 4 nucleated red cells per 100 white cells. The platelet count was 26,000, and many platelets were large and bizarre in appearance. The capillary-fragility test was negative. The red cells showed marked anisocytosis, poikilocytosis and polychromatophilia. Osmotic fragility of the red cells was normal. Urinalysis was negative. The blood nonprotein nitrogen was 39 mg., the sugar 100 mg., the serum bilirubin 2.3 mg., the uric acid 5.6 mg., the albumin 2.8 gm., the globulin 1.6 gm., and the phosphorus 5.6 mg. per 100 cc., and the alkaline phosphatase 7.2 Bodansky units. Cephalin flocculation was negative, thymol turbidity 1.4 units, and prothrombin time 24 seconds (50 per cent of normal), and there was no retention of bromsulfalein. The fecal excretion of urobilinogen, measured on 2 occasions, was more than 4 times the normal value. The Coombs test was negative. A biopsy of the sternum disclosed myeloid and megakaryocytic hyperplasia, but no fibrosis was seen in the sections examined. Smears of the bone marrow showed a predominance of erythroid elements. Roentgenograms of the chest, spine, skull and pelvis were normal.

The patient was given radiotherapy over the spleen, receiving 300 r without significant effect on the fever, size of the spleen or the blood picture; 7000 cc. of whole blood, administered over a period of 1 month, raised the hematocrit only to 31 per cent. Because of the evidence of hemolytic anemia and severe thrombocytopenia, splenectomy was decided upon even though the possibility of myeloid metaplasia was seriously considered. An additional 3000 cc. of blood, given during a 48-hour period, raised the hematocrit to 47 per cent. Splenectomy was performed without difficulty although the spleen weighed 2400 gm. On section there were many foci of myeloid metaplasia. Biopsy of the liver showed numerous islands of extramedullary blood formation. The patient was afebrile for 3 days after the operation, but after this time fever recurred. A small pleural effusion on the left side developed. Aspirated blood-tinged pleural fluid was sterile. There was gradual recession of the pleural effusion, but the fever persisted. Striking hematologic changes followed splenectomy. The platelet count rose to 58,000 within 48 hours. On the 4th postoperative day the hematocrit was 43.5 per cent, the white-cell count 20,300, and the nucleated red-cell count 4050. Thereafter, the hematocrit gradually declined, reaching 33.5 per cent on the 17th postoperative day. He received 4 pints of blood on the following 3 days, the hematocrit rising to 41 per cent. He returned to his home, where his general condition remained fairly good except for persistence of evening temperature elevations.

He was readmitted to the hospital 6 weeks after operation for reinvestigation of the fever. At that time he was ambulatory and complained of fever and weakness. The temperature was observed to rise to about 102°F. Signs of pleural effusion were subsiding. The liver seemed larger than it had been prior to splenectomy. The hematocrit was 31 per cent, and the white-cell count 18,100. Many studies were carried out in an effort to account for the fever, but no cause could be found other than the blood dyscrasia. The serum bilirubin at this time was 1.1 mg. per 100 cc., and fecal excretion of urobilinogen was well within the normal range. He was given 4 transfusions. At the time of discharge from the hospital almost 2 months after splenectomy the red-cell count was 3,640,000, the hemoglobin 10.8 gm. per 100 cc., the hematocrit 34.4 per cent, the mean corpuscular volume 95 cubic microns, the mean corpuscular hemoglobin 30 microgm., and the mean corpuscular hemoglobin concentration 31 per cent; the white-cell count was 24,600, with 12 per cent myelocytes 19 per cent juvenile and 26 per cent mature neutrophils, 1 per cent eosinophils, 4 per cent basophils, 7 per cent lymphocytes and 31 per cent monocytes. There was marked anisocytosis of the red cells, some stippling and occasional Howell-Jolly bodies and polychromatophilia. The nucleated red-cell count was 2700. The platelet count was 81,000, and there were many large and abnormal platelets. It seemed clear that splenectomy had been followed by cessation of the hemolytic process and elevation of the platelet count.

Discussion

There are two current theories concerning the etiology of the myeloid metaplasia syndrome. One, expressed by Donhauser,[6] is that this disorder is brought about by interference with bone-marrow

TABLE 1. *Data in 29 Patients with Agnogenic Myeloid Metaplasia Subjected to Splenectomy since 1937.*

CASE No.	AUTHOR	RED-CELL COUNT		HEMOGLOBIN		WHITE-CELL COUNT		MYELOCYTES		NUCLEATED RED CELLS	
		BEFORE SPLENECTOMY $X10^6$	AFTER SPLENECTOMY $X10^6$	BEFORE SPLENECTOMY gm./100 cc.	AFTER SPLENECTOMY gm./100 cc.	BEFORE SPLENECTOMY $X10^3$	AFTER SPLENECTOMY $X10^3$	BEFORE SPLENECTOMY %	AFTER SPLENECTOMY %	BEFORE SPLENECTOMY /100 white cells	AFTER SPLENECTOMY /100 white cells
1	Jackson et al.[3]	0.82	—	3.1	—	27.0	—	10	—	Many	—
2	Jackson et al.[3]	4.1	No significant change	—	—	53.0	No significant change	13	No significant change	6.0	No significant change
3	Jackson et al.[3]	4.5	3.0	12.5	—	15.0	70.0	6	10.0	—	Occasional
4	Reich and Rumsey[12]	2.5	—	(46%)	—	7.6	—	6	—	Many	—
5	Reich and Rumsey[13]	3.6	2.2	(75%)	8.0	13.8	4.8	14	0	2.0	4.0
6	Reich and Rumsey[14]	3.0	5.2	(59%)	16.0	21.5	41.0	0	13.0	1.0	0
7	Reich and Rumsey[14]	4.2	4.2	(85%)	13.5	7.5	134.0	2	6.0	0	6.0
8	Brewster and Wollenman[17]	1.0	0.7	3.6	—	10.1	79.0	5	—	5.5	17.5
9	Polowe[18]	4.0	Normal	(61%)	—	7.2	Normal	2	—	0	—
10	Lindeboom[19]	4.94	3.66	(80%)	(70%)	4.5	13.2	2	3.5	(2%)	(40%)
11	Heller et al.[4]	3.3	3.2	(58%)	(58%)	20.0	59.0	0	22.0	0	0
12	Levinson and Limarzi[20]	0.89	0.64	2.1	1.5	13.95	14.5	23	8.0	3.0	1.0
13	Edwards[21]	—	—	—	—	—	—	—	—	—	—*
14	Edwards[21]	2.7	—	(42%)	(80%)	0.4	40.0	0	Many	0	Many
15	Downey and Nordland[22]	2.96	3.2	(43%)	(44%)	22.0	79.7	16	14.0	42.0	38.0
16	Duvoir et al.[23, 24]	3.4	2.9	(80%)	(70%)	6.0	37.5	0	1.0	2.0	0
17	Carpenter and Flory[25]	2.43	2.3	7.5	8.3	3.1	49.0	9	6.0	9.0	7.0
18	Florentin et al.[26]	2.0	3.3	5.2	6.2	1.4	26.0	0	0	0	0
19	Bukh and With[9]	—	3.08	(100%)	(39%)	—	24.3	—	0	—	6
20	Waitz and Warter[27]	4.7	4.2	(72%)	(70%)	3.0	18.0	5	0	4.0	0
21	Skinner and Sophian[28]	1.6	4.5	(16%)	14.0	16.8	10.0	0	0	Many	0
22	Kjerulf-Jensen[29]	3.6	5.4	(51%)	(94%)	7.7	11.0	0	3.0	0	100.0
23	Kjerulf-Jensen[29]	—	3.2	(60%)	(60%)	15.0	17.0	0	1.0	0	32.0
24	Dustin[30]	2.7	2.04	—	(63%)	5.0	15.0	0	14.0	0	30.0
25	Green, Conley, Ashburn and Peters	2.7	2.96	7.4	9.3	1.95	14.8	0	3.0	0	58.0
26	Green, Conley, Ashburn and Peters	—	5.34	(85%)	15.0	12.0	30.4	0	8.0	0	2.5
27	Green, Conley, Ashburn and Peters	—	2.78	—	9.7	—	21.7	—	2.0	—	6.0
28	Green, Conley, Ashburn and Peters	3.96	4.29	12.6	12.3	7.25	11.7	0	0	2.0	0
29	Green, Conley, Ashburn and Peters	2.94	3.64	7.9	10.8	2.9	24.6	12	12.0	4.0	(2700 per cubic millimeter)

*In addition to myeloid metaplasia.

TABLE 1 (*Concluded*).

CASE NO.	PLATELETS		COURSE AFTER SPLENECTOMY	PATHOLOGY		TOTAL KNOWN DURATION OF DISEASE	REMARKS
	BEFORE SPLENECTOMY $X10^3$	AFTER SPLENECTOMY $X10^3$		SPLEEN*	BONE MARROW	yr.	
1	—	—	Death from generalized peritonitis in 3 days	Weight, 1240 gm.	Hyperplasia	6	Jaundice for 6 yr.; probably chronic hemolytic anemia.
2	—	—	Survival for 2 yr.; death from septicemia	Weight, 1100 gm.; fibrosis.	"Cellular"	21	No apparent effect of splenectomy
3	—	—	Survival for 3½ mo.; death from bronchopneumonia.	Weight, 745 gm.	Not reported	8	Striking rise in white-cell count but no improvement in anemia
4	—	—	Survival for 5 yr.; death from cardiac failure and terminal endocarditis.	Weight 2850 gm.	Osteosclerosis	5½	No apparent effect of splenectomy; severe anemia persisted, requiring many transfusions.
5	—	—	Patient surviving at time of report (2½ yr. after splenectomy)	Weight, 1800 gm.	Fibrosis	10½	No apparent effect of splenectomy
6	—	—	Patient surviving at time of report (3½ yr. after splenectomy)	Weight not reported	Not examined	4½	Splenectomy of possible benefit
7	—	—	Patient surviving at time of report (1 yr. after splenectomy)	Weight, 1895 gm.	Fibrosis	6	No important effect of splenectomy except marked rise in white-cell count and increase in nucleated red cells
8	—	—	Death 12 days after splenectomy	Weight, 710 gm.	Hyperplasia	1(?)	Severe hemolytic anemia, requiring many transfusions; no improvement after splenectomy.
9	60	Normal	Patient surviving and well 5 yr. after splenectomy	Weight 1060 gm.	No biopsy	10	Severe thrombocytopenic purpura complicating pregnancy; "cured" by splenectomy.
10	—	—	Patient surviving at time of report (13 mo. after splenectomy)	Weight, 1680 gm.	Not reported	4	No apparent effect of splenectomy except increase in white-cell count and nucleated red cells
11	—	—	Patient surviving at time of report (2 yr. after splenectomy)	Weight, 1000 gm.	Not reported	3	No apparent effect of splenectomy except increased white-cell count and higher proportion of immature cells
12	—	—	Survival for 1 mo.; death from left-upper-quadrant abscess, septicemia and pericarditis.	Weight, 520 gm.	Hyperplasia	3	No apparent effect of splenectomy; patient died from complications.
13	—	—	Patient surviving and said to be improving 4 mo. after splenectomy	Weight not reported	Not reported	Not reported	Marked improvement in blood picture and health followed splenectomy
14	—	—	Patient surviving and much improved at time of report (2 yr. after splenectomy)	Weight not reported	Sclerosis	2	Severe hemolytic anemia; much improved by splenectomy.
15	"Low"	Many	Death from ascites 3 mo. after splenectomy	Weight, 7000 gm.; fibrosis.	Areas of hypoplasia and hyperplasia	4½	Striking increase in platelets after splenectomy
16	—	—	Survival for 43 mo.; death from internal hemorrhage.	Weight, 1200 gm.	Normal (aspirated specimen)	11½	Marked bleeding tendency in spite of increase in platelets to over 4,000,000
17	—	—	Survival for 32 mo. after splenectomy; death from miliary tuberculosis.	Weight, c. 3000 gm.	Osteosclerosis and fibrosis	3	Marked rise in white-cell count after splenectomy, without improvement in anemia, for which transfusions required
18	—	—	Survival for 2 mo. after splenectomy; death from pneumonia.	Weight, 1600 gm.; fibrosis.	Not examined	2⅝	No apparent effect of splenectomy except rise in white-cell count
19	—	—	Patient committed suicide 9 mo. after splenectomy	Weight, 1250 gm.	Hyperplasia	1	Hypochromic anemia, attributed to bleeding peptic ulcer
20	—	—	Survival for 7 mo. after splenectomy; death from obstructive biliary-tract disease.	Weight, 2200 gm.	Myelofibrosis	6	Great symptomatic improvement after operation; death from unrelated causes.
21	—	—	Patient surviving and much improved at time of report (5 yr. after splenectomy)	Weight, 1080 gm.	"Cellular"	5½	Rapid clinical and hematologic improvement after splenectomy
22	—	—	Patient surviving at time of report (6 yr. after splenectomy)	Weight 1850 gm.	Erythroid hyperplasia (aspirated specimen)	9	Patient much improved after splenectomy
23	—	—	Patient surviving at time of report (2 yr. after splenectomy)	Weight, 1330 gm.	Erythroid hyperplasia (aspirated specimen)	3	No apparent effect of splenectomy except increase in nucleated red cells
24	—	—	Survival for 6 yr. after splenectomy; death in coma of apparently unrelated cause.	Size of spleen, "enormous"	Myelofibrosis	6	No apparent effect of splenectomy except increase in white-cell count and in immature red and white cells
25	38	450	Survival for 4¾ yr. after splenectomy; death from hemorrhage after gastrectomy for peptic ulcer.	Weight, 1500 gm.	Myelofibrosis with areas of hyperplasia	5 (at least)	Thrombocytopenia immediately subsided after splenectomy
26	—	1580	Patient surviving and in good health at time of report (4½ yr. after splenectomy)	Weight, 1500 gm.	Myelofibrosis and osteosclerosis, with areas of hyperplasia	6	No effect of splenectomy except increase in white-cell count and in immature red and white cells
27	—	300	Survival for 20 yr. after splenectomy; death from cerebral thrombosis.	Weight, 900 gm.	Myelofibrosis and osteosclerosis, with areas of hyperplasia	20	No apparent effect of splenectomy
28	540	5000	Patient surviving and in good health at time of report (7¼ yr. after splenectomy)	Size "large"	Myelofibrosis, with foci of hyperplasia	7¾	No important effect of splenectomy
29	26	81	Patient surviving at time of report (2 mo. after splenectomy)	Weight, 2400 gm.	Myeloid and megakaryocytic hyperplasia	1	Hemolytic anemia and thrombocytopenia improved after splenectomy

function, with compensatory extramedullary blood formation in the spleen and liver. It is well known that extramedullary blood formation may occur in certain cases in which bone-marrow function is impaired — for example, in osteopetrosis and carcinomatous replacement of the bone marrow. Supporters of this view attribute the leukoerythroblastic peripheral blood picture to the absence in the metaplastic tissue of a regulatory mechanism normally present in the marrow.[7] If this theory were correct, it is obvious that splenectomy or splenic irradiation would be contraindicated and would lead to production of more severe anemia. Support for this hypothesis is apparently provided by the reported high mortality after splenectomy.[2, 3, 10]

A considerably different theory, originally proposed by Vaughan and Harrison,[11] holds that "agnogenic myeloid metaplasia," like polycythemia vera and "megakaryocytic leukemia," is a proliferative disorder of the primitive mesenchymal precursors from which the hematopoietic system takes origin. The idea that this abnormality is primarily a proliferative one has recently been supported by Heller and his associates,[4] Rosenthal[12] and Dameshek.[13] It is known that enormous enlargement of the spleen may occur at a time when the bone marrow is cellular and that myelofibrosis may be a late development.[14] In reported cases of the disease the bone marrow has been variously hypoplastic, fibrotic and hyperplastic.[2] In cases of extramedullary blood formation associated with osteopetrosis or replacement of bone marrow by tumor, the extreme hepatosplenomegaly seen in "agnogenic myeloid metaplasia" is not usually encountered. Furthermore, numerous cases of polycythemia vera have terminated with a clinical and hematologic picture indistinguishable from the syndrome of myeloid metaplasia. In addition, fibrosis of the bone marrow occurs in some cases of unequivocal leukemia.[15] It is of interest that peptic ulcer and gout, commonly encountered in patients with polycythemia vera, also occur with increased frequency in patients with "agnogenic myeloid metaplasia."

Evidence bearing on the nature of the disorder is provided by observations on the effects of removal of the spleen. The popularity of the compensatory-metaplasia theory has led to a general notion that splenectomy is often followed by disastrous consequences because of the removal of a major blood-forming area.[7] Nevertheless, splenectomy has been performed in a sufficient number of cases to make possible a reasonably satisfactory appraisal of the results of this operative procedure. Hickling[3] reviewed the reported cases of the syndrome in which splenectomy was performed prior to 1937. Fifteen of the 27 patients died within the first four weeks, and 12 within four days of splenectomy. Death occurred in the majority of cases in the immediate postoperative period, undoubtedly reflecting the hazard of a formidable surgical procedure in seriously ill patients. However, in more recent years splenectomy has become less hazardous. Fisher and his associates[16] have pointed out that the operation in patients with leukemia carried a high operative mortality before 1940, but lately the risk has been greatly reduced because of improved surgical technic and postoperative care. It is noteworthy that the patients in Hickling's series who survived the immediate postoperative period did not give impressive evidence of deterioration of the blood picture, and 1 patient lived for eight years; Hickling did not attribute the high mortality to loss of the spleen per se. Since his report many other patients with "agnogenic myeloid metaplasia" have been subjected to splenectomy. The data in 29 cases are summarized in Table 1. It is apparent that the postoperative mortality in this more recent series is far below that reported by Hickling. Only 3 of 29 patients died within the first month of operation — 2 of postoperative infections. Fifteen patients are known to have survived for periods in excess of two years, and 8 for four years. Thirteen patients were still alive at the time of last report. Deaths after the immediate postoperative period were attributable to a variety of conditions, including miliary tuberculosis, biliary-tract disease, cardiac failure, cerebrovascular accident and suicide. There was no evidence that the course of the disease in most of the cases in which splenectomy was performed was appreciably different from that in patients not subjected to operation. Comparison of preoperative blood values with those obtained at intervals after the operation did not suggest that splenectomy resulted in decreased blood formation. Splenectomy was often followed by a striking increase in the white-cell and platelet counts and in the number of nucleated red cells in the peripheral blood.

Although there is little evidence that loss of the spleen per se was harmful to patients with this disorder, it is apparent that no benefit was derived in most cases. However, in occasional cases dramatic clinical and hematologic improvement followed splenectomy. In some cases in which hemolytic anemia was a prominent feature, splenectomy was beneficial (Table 1, Cases 14 and 29). In others thrombocytopenia was improved (Table 1, Cases 9, 15, 25 and 29). In the 5 cases described in the present report, no harmful effects of splenectomy were observed, and in 1 there was definite improvement.

The clinical course of the syndrome is variable. Some patients live for many years, little troubled by their disease, whereas others have a rapidly fatal outcome. There is no evidence that splenectomy has any effect on the general course of the disease. When abnormal bleeding is the result of severe thrombocytopenia, the operation is very likely to result in elevation of the platelet count and improved hemostasis. However, abnormal bleeding sometimes occurs in this disorder in patients with normal or ele-

vated platelet counts. In these cases splenectomy is without beneficial effect. Severe thrombocytopenia seems to be the outstanding indication for splenectomy in patients with myeloid metaplasia. The procedure has been less regularly effective in controlling hemolytic anemia, and in some cases the hemolytic process has apparently been unaltered (Table 1, Case 8).

It is clear that splenectomy is not indicated in the majority of cases of "agnogenic myeloid metaplasia." The enormous size of the spleen, the poor general condition of the patient and the bleeding tendency that is often present may make the operative risk appreciable. Furthermore, most patients do not derive benefit from removal of the spleen. However, it is equally clear that splenectomy does not often lead to failure of the blood-forming system. In certain carefully selected patients the operation may be of definite therapeutic value.

Summary and Conclusions

Five cases of "agnogenic myeloid metaplasia" were studied after splenectomy. In no case did the operation have a deleterious effect, and 1 patient showed hematologic improvement. A review of the literature fails to confirm the belief that splenectomy leads to disastrous effects because of the removal of a large blood-forming area. The operative risk is appreciable because of the surgical hazard, and most patients show no improvement. However, occasional patients derive definite benefit, particularly when there is severe thrombocytopenia or hemolytic anemia.

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COMPLICATIONS INDUCED BY ANTIMICROBIAL AGENTS*

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THE widespread use of antimicrobial agents may have completely resolved many perplexing problems in the field of infectious diseases but it has also created many new and even more perplexing ones. Among these are the various untoward effects, which have been increasing steadily; some are directly toxic, some are allergic, and others are related to the biologic activities of the chemotherapeutic substances. The reasons for an increased prevalence of undesirable sequelae to chemotherapy are mainly three: the increase in the number of antimicrobial agents, each of which may produce such reactions; the increase in the number of people treated so that, even had the incidence remained constant, the total number of reactions would have risen; and repeated administration of single or multiple agents so that ever-increasing numbers of people are conditioned to show various manifestations of hypersensitivity when exposed to these drugs.

The list of the undesirable effects actually observed and attributed to therapy with the widely used antimicrobial agents is long and varied and involves most of the organ systems. Not all the complications have occurred with each of the chemotherapeutic substances, and some have been noted with only one or another of them. Moreover, the incidence of the individual reactions varies widely both among the different agents and for any one of them. Only some of the salient features of these side effects can be touched upon in this brief presentation; for convenience they are discussed in relation to the different organ systems involved.

CUTANEOUS MANIFESTATIONS

The most common untoward reactions to systemic administration of antimicrobial agents are manifested in the skin by a large variety of lesions; most of them are probably a result of sensitization and are frequently accompanied by fever and pruritus. These lesions may occur either during therapy or soon after the administration of the same or a related agent is resumed. They may be transient, but most often they increase in intensity and change their character, or are followed by more serious consequences if the treatment is continued after the eruptions appear.

The cutaneous lesion most frequently seen with all the agents is a morbilliform eruption; less frequent are the scarlatiniform, urticarial, vesicular or bullous eruptions, which may be very incapacitating. Purpuric lesions, with or without thrombocytopenia, may also occur; although some of these are merely superficial or perhaps manifestations of serum-sickness-like reactions, blood vessels may be involved, occasionally giving rise to extensive, severe necrosis of large areas of skin. Skin lesions may also resemble the various forms described under the term erythema multiforme. Some agents, notably sulfathiazole, produce the typical lesions and distribution of erythema nodosum accompanied by conjunctival injection and episcleritis. The most severe manifestation in the skin, however, is exfoliative dermatitis, which may follow the morbilliform or scarlatiniform lesions when the offending agent is not removed; it may be extremely incapacitating and is sometimes fatal.

Local inflammatory reactions may occur at the sites of injections; they vary in frequency with different agents and sometimes with various lots of preparations of the same agent. They may be due to the specific irritating character of the broad-spectrum antibiotic injected or to the hypertonicity of the solutions, as when large doses of penicillin and streptomycin are given in small volumes of fluid. Sometimes the high concentration of cations or anions of these two drugs respectively may be the cause.

In the management of the skin lesions the most important measure is the discontinuance of the drugs and promotion of their elimination. The antihistaminic drugs may be helpful, particularly in combating the pruritus, and occasionally they reduce the severity of lesions or limit their spread. ACTH and cortisone may be of benefit and are sometimes even life saving in cases of exfoliative dermatitis or in patients with severe and extensive urticarial or bullous eruptions. These hormones also relieve the pruritus and edema, but they have not proved very helpful in either the prevention or the limitation of most of the other lesions of the skin.

ORAL LESIONS

As many as 33 different oral manifestations have been reported[1] among the reactions to antimicrobial agents but most often with the broad-spectrum antibiotics, — aureomycin, chloramphenicol, terramycin, — and are sometimes described as ulcera-

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The subject matter of this paper was presented under this title at the Eleventh Annual New England Post-Graduate Assembly, October 28, 1952, and also under the title "Untoward Reactions to Chemotherapy" at the Seventh Post-Graduate Lecture Course of the Massachusetts Medical Society, March 3, 1952. The essentials of both presentations are summarized here at the request of the editor.

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tive or vesicular stomatitis. The chief symptoms are dryness, burning, soreness and itching of the mouth and tongue. The buccal mucous membranes may be red and inflamed, with or without vesicles; the tongue may be red, smooth and shiny, swollen, furred or denuded. Angular stomatitis (cheilosis) has been ascribed to riboflavin deficiency during antibiotic therapy, but administration of this vitamin with or without other members of the vitamin B complex in large amounts has usually failed to cure the lesions so long as antibiotic therapy was continued. The black, hairy tongue or the brown-coated tongue has been attributed to overgrowth of yeast-like organisms, although these cannot always be seen in smears or grown in cultures. To be sure, monilia are cultured from the mouth more readily than usual, but they are only infrequently associated with symptoms attributable directly to that organism.

Serious or distressing oral lesions are observed much more often with lozenges or troches than with systemic treatment either oral or parenteral, stomatitis or glossitis or both having been noted in 18 per cent of patients receiving antimicrobial agents, including sulfonamides, in these forms. As with cutaneous manifestations, the removal of the offending agent — that is, the discontinuance of this topical therapy — is the most important therapeutic measure. There may be some question whether local oral treatment with lozenges or troches is to be recommended for any purpose, because of these reactions, because of the greater danger of sensitization from these dosage forms and because there is serious doubt about the efficacy of any of these agents given in this manner.

Other Manifestations of Hypersensitivity

In addition to the lesions of the mouth and skin already mentioned, a number of manifestations are readily identified as specific reactions of hypersensitivity to antimicrobial agents. One of these is "drug fever"; this may occur as the only reaction to sensitization or may precede or accompany other lesions, particularly rashes. When fever is the only untoward effect, cessation of therapy will usually bring the temperature down to normal levels within a few hours if the agent is rapidly eliminated, or after a longer period if the drug is eliminated slowly. Reinstitution of treatment with the same agent will usually result in rapid recurrence of fever, with or without rashes.

Contact dermatitis has been observed with many of the antimicrobial agents, particularly with penicillin and streptomycin, in persons (pharmacists, nurses and doctors) who handle these substances and who themselves have not received any of them by injection, or taken any of them by mouth. This dermatitis usually involves the hands and face and may be accompanied by edema and vesiculation or eczema, and in some cases there is also allergic rhinitis and asthmatic breathing. The experience of the past few years has indicated quite definitely that the applications to the skin of ointments and oily suspensions of various antimicrobial agents produces the highest incidence of local and systemic sensitization. One should therefore carefully consider in any clinical situation the possibilities of parenteral or oral administration of antimicrobial drugs in the management of various types of infectious skin lesions before embarking on a program of continued application of one or another of the antimicrobial agents to the skin, particularly when the substance is dissolved in an oil or fat.

Other typical reactions of hypersensitivity, including angioneurotic edema, reactions similar to the Arthus phenomenon, "serum sickness" and acute anaphylaxis, have followed the use of various antimicrobial agents, particularly penicillin and streptomycin. Angioneurotic edema, with swelling of the lips, tongue, face and periorbital tissues, accompanied sometimes by difficulty in breathing, has occurred after injection or exposures to these agents. Local edema and inflammation, sometimes followed by necrosis (Arthus reactions) at the site of subcutaneous or intramuscular injections, have been described, increasing in intensity with successive subcutaneous or intramuscular injections unless treatment is stopped.

All the manifestations that are known to follow the injection of horse serum or other foreign serums and are included under the name "serum sickness" have been observed after injections of penicillin and less often after streptomycin. These reactions include fever, urticaria, eosinophilia and sometimes purpura, arthralgia, lymphadenopathy and splenomegaly. There may also be edema, albuminuria and microscopic hematuria. This type of reaction has most often followed the use of repository types of penicillin, first those given in beeswax and oil and later procaine penicillin preparations, particularly those in which this ester is suspended in oil and aluminum monostearate. The reaction may begin after one week or longer of continuous treatment with penicillin or streptomycin or other agents, but sometimes the first manifestations are delayed for as long as a week or two after the last dose has been given.

The most dangerous reaction, of course, is that of acute anaphylaxis. Fortunately, only very few authentic cases of this type of reaction have been reported, and these occurred after single injections in "allergic" persons who had previously been exposed to the agent. There have been isolated fatal cases from this cause in which it was definitely shown that death was not related to possible intravenous injection of an insoluble preparation.

At least two serious chronic systemic diseases — namely, periarteritis nodosa (polyarteritis or polyvasculitis) and disseminated lupus erythematosus — have recently been recognized as reactions of hyper-

sensitivity and have been attributed in some cases to the use of antimicrobial agents. They were first described in relation to sulfonamides and are occasionally ascribed to treatment with penicillin and streptomycin and perhaps to other antibiotics. They appear to be the result of continued or repeated administration, especially in "allergic" persons who show other manifestations of hypersensitivity to these and other agents. A third serious reaction, acute hepatitis (hepatosis), with rapid enlargement of the liver and jaundice, has been observed in occasional patients in whom treatment with the offending agent, particularly sulfathiazole, has been continued in the face of drug fever and rashes; this is fortunately a rare occurrence, but its relation to drug toxicity is indicated by the rapid improvement that follows the discontinuance of the agent before irreversible damage has occurred and the rapid relapse when the drug is again exhibited.

For the most part, the reactions of hypersensitivity, including drug fever, are highly specific for the particular substance used, but in certain cases they may be elicited by closely related agents. About 15 per cent of patients sensitized to one sulfonamide drug will react to any other sulfonamide; however, almost all patients sensitized to sulfadiazine will react to both sulfamerazine and sulfamethazine,[2] and the reverse is also true; all three of these drugs are pyrimidine derivatives of sulfanilamide. Penicillin O will elicit a reaction in more than a third of the patients sensitized to penicillin G and vice versa. Terramycin has been described as eliciting a cross-fixed reaction in a patient previously sensitized to aureomycin. On the other hand, dihydrostreptomycin may be given to most patients who have previously been sensitized to streptomycin and vice versa, although a reaction occasionally occurs with one when the patient has been previously sensitized to the other.

The prognosis in cases of sensitization to antimicrobial agents is variable and often unpredictable. Many patients, and perhaps most of those who have had fever and rashes during or after penicillin therapy and who have been considered to be sensitive to that agent, have subsequently been given full courses of treatment without any reaction. This may be due to differences in the nature of the impurities responsible for the original reaction. It has been particularly true when the sensitization has been the result of a repository type of preparation such as procaine penicillin, with or without aluminum monostearate, and a purified sodium or potassium salt of crystalline penicillin G was later used. Moreover, patch tests and intracutaneous or conjunctival tests have also given variable results, which have not always correlated with the effects elicited on subsequent administration of the agent. A generalized hypersensitivity reaction from a skin test with penicillin has been reported, so that some risk may be involved in such a test. Attempts to desensitize patients have also been made and considered successful by some workers; however, such successes are open to the criticism that the patient may not actually have been seriously sensitized to the product used in the desensitization procedure or for the subsequent treatment.

In the management of the acute delayed reactions of hypersensitivity the antihistaminics sometimes give partial or complete relief from the pruritus associated with the skin lesions and may reduce the intensity or prevent the extension of the lesions, but they do not affect the arthrosis, lymphadenopathy or renal lesion. ACTH or cortisone may be expected to relieve the itching and joint pains although reports of such usage are still too few and are not uniformly favorable. The possibility of an acute anaphylactic reaction in a person with an allergic history who has previously been exposed to the agent to be used indicates that the greatest caution must be exercised in the initiation of subsequent courses of treatment with the same agent or even in testing the patient for sensitivity to that agent. In such a case it is essential that the physician be present at the time when the test dose or the first dose is given and be prepared for appropriate measures to tide the patient over any acute asthmatic or vascular type of anaphylactic reaction.

Gastrointestinal and Hepatic Complications

Disturbances in the function of the digestive tract are seen most frequently after the use of the broad-spectrum antibiotics. The oral administration of aureomycin, terramycin or chloramphenicol may be followed by nausea, with or without vomiting, and by diarrhea of varying severity. These are probably due to a direct irritating action of the agents on the bowel; reduction in the dose or administration of the antibiotic with milk or food may lower the incidence and severity of these gastrointestinal complaints. It is well to bear in mind that penicillin and streptomycin given by mouth in comparable doses may also produce heartburn, nausea and vomiting and diarrhea. The last may also result from the use of large doses of the poorly absorbed sulfonamide drugs — namely, sulfasuxidine and sulfathalidine.

Serious, however, are the severe diarrheas, with the liquid stools containing large amounts of mucus and pus, which may be followed by high-grade dehydration and severe prostration. These have been noted after the use of aureomycin, terramycin and sometimes with chloramphenicol. Some of these diarrheas have been associated with the presence of coagulase-positive and hemolytic strains of *Staphylococcus aureus*, which have been found in large numbers or even in pure cultures in the stools; these probably represent cases of acute staphylococcal enteritis resulting from the change in the

bacterial flora of the bowel produced by the administration of one of these agents. Acute colitis, either ulcerative or membranous, in which the intestinal flora consists practically exclusively of either *Staph. aureus* or strains of pseudomonas or proteus has also been noted after the administration of some of the broad-spectrum antibiotics, although this reaction has been rare. Some deaths have resulted from these severe intestinal disturbances.

Acute monilial stomatitis and pharyngitis that sometimes accompany the administration of some of the antibiotics may extend down to the lower reaches of the gastrointestinal tract, and such an extension has perhaps been the direct cause of some deaths. This, however, has been noted primarily when the antibiotics have been used for long periods in debilitated patients, particularly children with pulmonary viscoidosis (pancreatic fibrosis), or in patients with acute leukemia who have been treated with folic acid antagonists.

The liver has also been occasionally affected in patients treated with antimicrobial agents. Jaundice and even acute yellow atrophy were well known toxic reactions to the administration of sulfanilamide; this was apparently a chemical hepatitis and was associated with decreased prothrombin early in the course of the reaction. Liver damage has not been a feature of the use of the subsequent sulfonamide drugs except as already noted. Although jaundice and hepatitis have followed the administration of streptomycin, it has not been certain whether these cases were not in fact cases of so-called syringe hepatitis — that is, serum hepatitis. For the most part the problem of liver damage has been stressed in reports of the administration of aureomycin and terramycin, and to a lesser extent chloramphenicol; fatty changes in the hepatic cells have been noted after the intravenous injection of excessive doses of these drugs both in mice and in human beings. Such changes have not been noted when the ordinary doses of 1 or 2 gm. a day are given by mouth to patients or to normal human subjects. On the contrary, aureomycin has been reported to be beneficial in the management of acute hepatic disorders in which hepatic necrosis is a feature. Moreover, it is difficult to determine in these cases to what extent dietary disturbances and infections are responsible either directly for the fatty changes in the liver or in conditioning these changes when the antibiotics are administered. Similar changes have been observed in dogs with prolonged administration of streptomycin. They are reversible as soon as the drug is discontinued.

In connection with the liver it should be borne in mind that urobilinogen may be absent from the urine and feces during the course of administration of aureomycin or terramycin by mouth. This is supposed to be due to the reduction in the types of organisms in the flora of the bowel that are responsible for the conversion of bilirubin to urobilinogen. Bilirubin is present, however, in abundance in the stools and in normal amounts in the serum. The recognition of this artefact is important in the differential diagnosis of intrahepatic disease and obstructive lesions in the biliary system. Liver function is not impaired in patients receiving the drugs by mouth who do not have infections or dietary deficiencies.

Urinary-Tract Complications

Serious lesions in the urinary tract have been observed during or after the administration of certain of the antimicrobial drugs, notably the sulfonamides. With an inadequate urinary output even the most soluble of the sulfonamides may lead to the production of hematuria and crystalluria, each of which may be detectable only on microscopical examinations of the urine. When this occurs, either the drug should be temporarily stopped or, if renal function is not yet impaired, the fluid intake should be increased so that the urine output for the twenty-four-hour period is at least 1200 cc. A serious form of this complication is the obstruction to the urinary flow produced by massive crystallization and stone formation within the kidney after the use of the poorly soluble sulfonamides in dehydrated patients when care is not taken first to hydrate the patient properly.

The most serious of the renal complications of sulfonamide therapy is production of acute glomerular lesions or of lower-nephron nephrosis; some of these are probably the result of hypersensitization to the drug and may follow the use of as little as 1 or 2 gm. of a sulfonamide that the patient has previously received and yet may result in complete renal shutdown persisting for as long as ten to fourteen days. This complication is not the result of crystallization of the drug in the renal papillae or pelvis and cannot be relieved by the same measures that are used to relieve ureteral obstruction from crystallization. Most important in the treatment of lower-nephron nephrosis is the exercise of great caution to prevent overhydration during the period of anuria.

Streptomycin may also produce renal difficulties, particularly when the urine is acid; albuminuria with increased numbers of casts may be present in such cases, and renal function may decrease after streptomycin administration in patients with underlying renal disease. The broad-spectrum antibiotics, in general, have been free of harmful effects to the kidney, and this is also true of penicillin. On the other hand, the less commonly used agents — polymyxin, bacitracin and neomycin — have a primary toxicity for the kidney. They cause albuminuria, casts, hematuria and reduction in renal function that is progressive until these drugs are discontinued. Fortunately, if the damage has not progressed too far, these reactions are reversible. At present polymyxin, bacitracin or neomycin should be re-

served for use only in serious types of infections in which other less toxic chemotherapeutic agents have failed to afford relief.

Effects on the Nervous System

A variety of untoward reactions referable to the nervous system have been noted. The intramuscular administration of concentrated solutions of some of these drugs may result in the introduction of the agent into a peripheral nerve and give rise to a chemical injury, producing sensory and motor changes that may persist for a long time. Peripheral neuritis has followed the prolonged treatment with broad-spectrum antibiotics and has been attributed, though without adequate proof, to vitamin deficiencies. Peripheral neuritis was also noted during the early clinical trials with sulfamethylthiazole, and this complication was responsible for the failure to permit the general use of the agent. Paresthesias of the hands, tongue and circumoral areas have been caused by streptomycin but have been particularly prominent even during the early course of treatment with polymyxin.

The most frequent of the neurologic disturbances, however, is damage to the eighth cranial nerve. Involvement of the vestibular branch of this nerve occurs most often with streptomycin, and the frequency and severity of the resulting disturbance are proportional to the dose and duration of streptomycin treatment. The auditory nerve has been affected more frequently with dihydrostreptomycin and even more so when neomycin is used. The ataxia and hearing loss from the use of streptomycin or dihydrostreptomycin in the treatment of tuberculosis have been minimized by the use of the intermittent regimen for prolonged therapy with the administration of streptomycin twice a week and para-aminosalicylic acid daily.

Diffuse and severe encephalitis and mental disturbances have been observed in some patients treated with some of the sulfonamide drugs. Toxic encephalopathy has also followed the administration of streptomycin, and toxic psychoses have been reported from sulfonamides and, in rare cases, from penicillin or from the use of other antimicrobial agents.

Considerable attention has recently been given to the untoward reactions that follow the intrathecal administration of penicillin or streptomycin. Local application of concentrated solutions of these antibiotics directly to cerebrocortical tissue results in serious disturbances. However, in our hands no difficulty from the intrathecal administration of penicillin and streptomycin has been observed. To be sure, large doses of these agents given intrathecally, either intentionally or by error, may produce marked increases in intracranial pressure, hyperirritability, twitching or convulsions and even coma and death. The maximum amount that may safely be introduced into adults at any one time is about 50,000 units of penicillin and 100 mg. of streptomycin, and smaller amounts should be used at first. These quantities are reduced for children roughly according to their body weights. Four additional precautions must be observed if serious reactions on the central nervous system are to be avoided: the drug should be diluted in at least 10 cc. of saline solution; the volume of spinal fluid withdrawn before the injection of the antibiotic should be in excess of this amount and should be withdrawn slowly; the injection of the diluted material should be made slowly, at a rate not exceeding 1 cc. per minute, and the final pressure should not exceed the normal; and, finally, if the intrathecal injection is followed within a few hours by a marked increase in signs of meningeal or cerebral irritation, lumbar puncture should be done, and spinal fluid withdrawn slowly if it is found to be under increased pressure.

Effect on Blood and Blood-Forming Organs

Acute hemolytic anemia was one of the early, unpredictable and serious complications of treatment with sulfanilamide, and this was sometimes rapidly fatal. The mechanism of the reaction is not entirely clear; it has been assumed to be a specific toxic effect of the drug or perhaps of some chemical contaminant in a particularly susceptible person. Interestingly enough, readministration of sulfanilamide at a later date to patients who previously had acute hemolytic anemia has been undertaken in some cases without recurrence of the reaction.

Mild anemias, either hypochromic or normochromic, have been described in patients who receive prolonged treatment with any of the antimicrobial agents; these have been seen perhaps more frequently with sulfonamides than with antibiotics. In many such cases it is difficult to delineate the part played by infection or by nutritional deficiencies in conditioning or causing these anemias. Eosinophilia may occur late in the course of treatment with antibiotics, but in the absence of skin lesions or other untoward effects it is difficult to determine whether the eosinophilia is a sensitivity reaction to the drug or is part of the recovery phase of the infection for which the drug was used. Granulocytopenias and thrombocytopenia have also been observed with streptomycin.

The most serious type of hematologic reaction, however, is the development of aplastic or hypoplastic anemia. This has occurred primarily in patients receiving prolonged or repeated courses of chloramphenicol, but not necessarily large doses. It has also been reported in 2 cases in which it was attributed to streptomycin. A number of deaths have resulted from this complication, some of them in patients in whom chloramphenicol was used in the treatment of relatively trivial conditions, such as mild respiratory infections or skin diseases, in which the drug could not be expected to have any

favorable influence. The bone marrow in these cases showed hypoplasia of all the marrow elements, and the peripheral blood demonstrated reduction of all of the myeloid elements (red cells, polymorphonuclears and platelets); the immediate cause of death has usually been bleeding, either intracranial or gastrointestinal.

The sulfonamides and particularly the antibiotics have also been considered to be responsible for various changes in the blood-clotting mechanism. The data in this regard are contradictory and confusing. Seegers[3] has recently reviewed the literature on this aspect and concluded that the antibiotics now in general use, when given systemically in ordinary therapeutic doses, have not been conclusively shown to have any serious effect on the coagulability of the blood.

Miscellaneous Effects

Many varieties of reactions, in addition to those mentioned, have been attributed to the toxicity of antimicrobial agents; some of them may be mentioned briefly. When applied to tissues directly in tissue cultures, in supervital preparations or in studies of the respiration of tissues, concentrated solutions of the various antimicrobial agents have been shown to have a direct toxic effect; this has been manifested by inhibition of growth in tissue cultures, by inhibition of certain enzyme or other biochemical actions and by an antiphagocytic effect. In patients receiving some of these drugs in high concentrations, or when certain agents are applied locally, hemolysis has been noted (as with tyrothricin and aureomycin solutions), and sometimes necrosis of tissue has occurred at the site of injection.

Vitamin and other metabolic deficiencies have been described; many specific ones have been demonstrated in animals, but the only ones that have been authenticated in human beings are a negative nitrogen balance and an increase in excretion of riboflavin resulting from administration of aureomycin in moderate therapeutic doses by mouth. Electrolyte disturbances have been noted in some patients treated with streptomycin, but they have regularly been associated with viomycin, an agent that is effective in tuberculosis but has not received wide acceptance. Cyanosis used to be a common concomitant of sulfanilamide therapy; it has not been observed with any other sulfonamides or with any other antimicrobial agents. Therapeutic shock (Jarisch—Herxheimer reaction) has sometimes occurred early in the course of the penicillin treatment of syphilis. Pulmonary embolism has been noted with the accidental intravenous injection of some of the insoluble preparations of penicillin. Electrocardiographic changes, particularly T-wave inversion, have been part of allergic reactions to various drugs, including the sulfonamides and particularly penicillin. One may also speak of the primary or specific toxicity of some agents in certain persons; this is comparable to the primary toxicity of penicillin for guinea pigs.

Bacteriologic Effects and Their Consequences

Among the serious untoward reactions that may follow antimicrobial therapy with the agents in use today are the changes in the bacteriologic flora and the new infections that may occur during or after the administration of these agents. The types of organisms that become predominant and the types of infections that may arise are related to the specific antibacterial effects of the particular antibiotics. Thus, agents that tend to inhibit gram-positive bacteria will permit gram-negative ones to grow out when they are given; the opposite is true when agents active against gram-negative organisms are used. The normal bacterial flora in the throat, bowel or female genitals is thus altered in such a fashion that one or two organisms insensitive to the drug that is being used become predominant. Whether new infections occur only because certain organisms normally present as saprophytes, or in small numbers, increase numerically to a point where they become invasive or whether the mechanism is a more profound one involving changes in tissues or stimulation of bacteria to become invasive is still an unsettled question. The fact remains that a small but significant percentage of patients treated with chemotherapeutic agents become infected with different organisms from the one for which the drugs are originally given.

The organisms that have been observed to increase most frequently during therapy are *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Staph. aureus* and *Candida albicans* (monilia). Also, in young children *Haemophilus influenzae* may replace gram-positive coccal infections when penicillin is used in therapy. In patients with underlying pulmonary disease, the new infections may occur as a superimposed bacterial pneumonia, whereas urinary-tract infections may change their bacteriologic character.

Localized abscesses may occur at the site of penicillin injections. These are associated with organisms that are resistant to the antibiotic that has been injected; the most frequent ones are the coliform bacilli, *P. vulgaris* and *Clostridium perfringens* (*Bacillus welchii*). The source of these organisms may be contamination from the skin, or possibly even from the antibiotic injected, or from poor technic. The changes in the oral and intestinal flora may give rise to serious infections in the gastrointestinal tract such as those already mentioned; the staphylococcus has been the most important organism in this complicating infection, at least at the Boston City Hospital.

Perhaps potentially the most serious complication of the widespread use of penicillin and the other antibiotic agents has been the emergence and increase in prevalence of organisms that are resistant

to most or all of the agents that have been so used. This has been clearly demonstrated with the staphylococcus. At the Boston City Hospital during the first few years after the introduction of penicillin, 85 per cent of staphylococci isolated from all sources were moderately or highly sensitive to penicillin, and during the first year after the introduction of aureomycin, a similar or greater proportion of staphylococci were sensitive to that agent. Since then, there has been a steadily decreasing incidence of sensitive organisms or an increase in percentage of organisms highly resistant to both these agents so that during the latter part of 1951 and early in 1952 only 1 out of 4 strains of staphylococci isolated could be considered sensitive to penicillin; only about two thirds of the strains were sensitive to aureomycin, and an even smaller percentage were sensitive to terramycin.

The significance of this finding goes beyond that of the staphylococcus problem. The potentialities for the emergence of races of pathogenic bacteria that are resistant to the available antimicrobial agents by the continuous and widespread use of such agents has already been adequately demonstrated with the sulfonamides. Classic and well authenticated examples of this phenomenon are provided by the epidemics of severe infections with strains of the hemolytic streptococcus resistant to sulfadiazine that occurred during World War II at military installations in which this drug had been used continuously in prophylaxis and the progressive loss of the effectiveness of sulfonamide drugs in the treatment of gonorrhea after their widespread use in therapy of this disease. Physicians are now faced with a progressive increase in the proportion of strains of staphylococci that are totally resistant to penicillin and are increasing in resistance to the other widely used agents, as well as with the mounting prevalence and importance of infections with strains of proteus, pyocyaneus, various fungi and various coliform organisms, all of which are resistant to all the available antimicrobial agents, both in vitro and in the treatment of diseases.

Discussion

An attempt has been made to review the undesirable effects of the use of antimicrobial agents. Striking is the fact that none of the available chemotherapeutic substances are free of the potentialities of causing trouble. With some, like the sulfonamides, the risk of development of serious reactions is great; with others, like penicillin, it is relatively small in comparison with the marked beneficial effects of this agent in the disease for which it is useful. Two types of reactions are common to all — the development of hypersensitivity and the emergence and increase of antibiotic-resistant organisms, with the resulting production of superinfections by such resistant organisms.

It would be a gross misinterpretation of the purpose of this presentation to leave the impression that the therapeutic agents under discussion are only harmful and should therefore not be used, for to act on that impression would mean the loss of countless lives and the occurrence of untold pain and suffering from the many infectious diseases that the antimicrobial agents have almost completely conquered or relegated to relative insignificance. Although it would be desirable, to put this presentation in its proper perspective, to balance the long list of undesirable effects of the antimicrobial drugs with the much more formidable list of their great achievements, that is not the task that was set for this paper. Moreover, the triumphs of the "wonder drugs" have been adequately and repeatedly extolled in thousands of medical and lay publications, but the dangers and the harmful sequelae of their uses, and particularly of their abuses, have not yet been given sufficient prominence.

The fact that harmful effects may follow the use of these drugs should not discourage the physician from applying them when they are definitely indicated. It should, however, make him hesitant to employ them in cases in which indications for their use are either entirely absent or at most only slightly suggestive, lest a simple or mild disease be converted into a serious and potentially fatal one. Moreover, the appearance of reactions during the course of treatment does not always make the cessation of therapy mandatory when the drug used happens to be the only effective one available for the purpose required. The severity and type of the reactions, their expected course and the possibility of influencing them by proper management must all be weighed against the importance of the infection under treatment and the prospect of favorably influencing that infection by continued therapy with the same or another effective agent.

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THE AIMS OF CHILD REARING*

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THE pediatrician is a newcomer in the field of mental health. There is good reason for this. Until recent years he was occupied with more urgent matters. Infants were dying in large numbers — the infant death rate in America in 1900 was more than four times what it is now. Mothers — and doctors too — were more concerned about a loose bowel movement than a frustration. Breast feeding was regarded as part of a mother's job. In addition, breast milk meant protection, to some degree, against the very serious summer diarrhea. No one thought especially about the relation between breast feeding and mother love. Mother love and baby cuddling were taken for granted and were practiced widely without benefit of psychiatrist.

For the 9 out of 10 babies who survived the first year of life — in many communities it was considerably less than 9 out of 10 — the dangers from the common contagious diseases, such as diphtheria, measles, scarlet fever and whooping cough, were considerable.

A young man who wished to become a pediatrician twenty or thirty years ago had to be prepared to recognize and treat the various diseases he was to meet. This required training, and the budding pediatrician considered his education incomplete if it did not include an internship at a hospital for contagious diseases.

Before the newer knowledge of nutrition was developed infant feeding was an intricate mathematical science. Formulas were calculated for caloric needs and percentage of the various constituents with a precision that is now applied only to the calculation of electrolyte and fluid needs. Incidentally, I look forward to the day — not too far distant, I hope — when the daily balancing of fluid and electrolyte requirements will be considered with the same amused skepticism with which the precise calculation of dietary needs is now regarded.

It must also be remembered that formerly the country was not as rich as it is now and that the resources to pay for the extended periods of training that doctors at present get were not readily available. Then, too, young men were more eager to get out into practice. The practice of medicine was regarded as a highly desirable and respected outlet for the graduate of a medical school and not, as it often is at present, as a refuge for those who lack the wit or financial resources to undertake a full-time career.

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The medical horizon has certainly changed. The serious problems of life and death are much less frequent than formerly, and the pediatrician is devoting his time and interest more and more to the less urgent but nevertheless important problems of feeling and behavior aspects previously reserved for the parents, the religious adviser and the teacher.

Actually, the pediatrician is not the novice in the field of mental health that he may seem to be. No thoughtful person, interested in his work as the overwhelming proportion of physicians are, can have pass through his hands so many children and parents each day without getting a pretty good idea of how they both feel and behave and why. As a matter of fact the pediatrician used to be a good therapist — until he was frightened away by the psychiatrists, with their warnings about "doing harm" and "being superficial."

When parents turn to the physician with problems of child rearing they seek not only a common-sense opinion but also advice based on scientific observation. Unfortunately, relevant data are incomplete and often poorly digested. Unlike other branches of modern medicine, the field of mental health is dominated by inadequately documented rationalizations and is divided into schools of thought with their loyalties and antagonisms.

The conscientious physician is confused and troubled by points of view and concepts that are widely accepted by psychiatrists but do not fit his everyday experience. He reads about the dire effects of too little mother love, but what he sees much more often is the spoiled, overindulged child, the product of doting, permissive parents. He is told of the deprivation suffered by the child who is forced to suck on a rubber nipple instead of the mother's breast, but he sees, all the time, children, who had been nourished from the bottle in infancy, growing up into quite normal adults. He is warned about the dangers of frustration, but he knows that he himself has never achieved anything worth while without suffering many frustrations.

Some psychiatrists would interpret the doting, permissive behavior of parents as unconsciously motivated, and as a mask for hostility and rejection. This is undoubtedly true in certain cases, but parental overindulgence is so widespread that it would be necessary to postulate the well nigh universal application of this mechanism among American intellectuals, a premise that I cannot accept.

In much of the literature on mental health the young child is represented as a helpless creature, threatened by disaster and overwhelmed by a cruel environment against which he is defenseless. Like the heroine in the blood-and-thunder melodramas

of the not too remote past, the poor child no sooner extricates himself from one critical situation than he finds himself catapulted into another. An author[1] writes in the 1950 volume of the *Psychoanalytic Study of the Child:*

> Normally, the second-year child has already made some progress from the situation of trauma and helplessness to that of anticipation of danger. . . . But the child of this age is confronted with a vast array of overwhelming forces. Many of these are unpredictable and beyond his comprehension. He stands up and a nameless force throws him down. He climbs on the chair and the temperamental piece of furniture spills him to the floor. . . . Mama is pleased when he eats his carrots and displeased when he eats the contents of his potty. For these reasons no child, no matter how tenderly cared for, can escape anxieties. Danger is omnipresent. . . .
>
> Now, or earlier, he has submitted to toilet training for no better reason than that it pleases the mother. He willingly becomes partner to a fraud in which mother exclaims over each stool, growing ecstatic as mothers will, only to see this gift of love flushed indifferently down the toilet. To fear of loss of feces is added the danger that, through soiling, through refusal to defecate in the pot, he will lose his mother's love. We observe that, even in those cases where toilet training has proceeded without threats or coercion, the child may still perceive a threat through his observation of the fate of his own feces.

Can one really believe that normal child development is as hazardous — as tragic — as it is depicted by this author? Can one really believe that flushing a toilet is a traumatic experience for a child?

I ask indulgence for one more quotation — this time from the pen of Dr. Margaret Ribble,[2] who has been more widely quoted in the psychiatric literature than any other on the psychologic development of infants. She finds that danger lurks even in the simple task of diapering the baby:

> Unknowingly, in this way [by diapering] mothers teach their children to get attention which should come through other avenues of stimulation. The children thus develop emotional reactions which become deeply involved with the function of elimination.

There is, in much of the psychiatric literature on child rearing, a note of urgency, an all-or-none attitude, a take-it-or-else quality that is remote from the long-tested, objective methods expected of the scientific approach. Catch phrases are devised for ancient practices like "rooming in," "self-demand" and "natural childbirth," and their merits are debated widely in the daily press, on the radio and television and in popular books. Points of view are presented with a fervor that has no place in critical discussion. These warmhearted postulations may be swallowed by the credulous, but they serve only to antagonize the thoughtful. Suspicion is aroused by a method of presentation that is strange to those accustomed to the painstakingly documented concepts of scientific procedure.

It is true that general medicine also contains much that is controversial. Some everyday practices lack clear-cut demonstration; others have been shown to be useless; still others (like ill advised tonsillectomy) are actually harmful. With the best of intentions, in their eagerness not to overlook an organic ailment, physicians have created too much anxiety in parents by "overdiagnosis." It is unfortunate that the stress in teaching is mainly on not missing organic disease; no emphasis whatever is placed on the harm done by finding what is not there.

Moreover, even in this day, when new concepts and information are rapidly disseminated, there is, in the minds of men, a certain inertia and even active resistance to change that is not readily overcome. But an essential difference exists between the erroneous practices of general medicine and the fallacious teachings of child psychiatry. The concepts of general medicine have been built up slowly and laboriously through repeated testing in clinic and laboratory. Theories that are unproved or are not susceptible of proof are accepted tentatively, if at all, and they are discarded when found to be false. Many of the concepts of mental health, on the other hand, rest on a theoretical substructure that is considered inviolate. The tendency, here, is to discard or disregard the data if they do not fit the theory, or to distort the data to fit the theory.

Critique by the Anthropologists

In 1949 Orlansky,[3] an English anthropologist working at Yale, undertook an investigation of one of the basic tenets of psychoanalytic theory — namely, that experience in early childhood is an important factor in shaping adult personality. Orlansky points out that Freudian theory rests, for the most part, on data obtained from the psychoanalysis of adults, child analysts being concerned more with application of the theory than with its examination. The psychoanalyst obtains his information about normal child development by probing the mental processes of adults who come to him with their problems and from students of psychoanalysis. The validity of reconstructing childhood experiences from interviews with adults is questionable. According to Kris,[4] a psychoanalyst, Freud himself doubted his ability to distinguish between the fantasies of his patients concerning their childhood experiences and feelings and the actual recollection of events that had taken place. Moreover, the validity of drawing conclusions about normal psychologic development from a study of persons who present themselves for psychoanalysis is doubtful.

Orlansky focused his studies on infantile sucking, mothering, toilet training, restraint of motion and "frustration" and "aggression." Specific channeling of these infantile activities and reactions is said to lead to specific psychologic constellations in the adult. For example, overattention to toilet training is said to lead to a certain type of personality, and excessive restraint of motion to another type. His exhaustive survey of the literature failed to give convincing evidence in favor of any of these widely accepted concepts. He found no data in the literature to show that any specific personality change

resulted from too early toilet training or too late, or from too strenuous training or too mild.

Orlansky concludes that though, admittedly, childhood experience is important in the formation of personality, the major building of personality takes place after the first year or year and a half of life, and, therefore, that the contribution of infantile experience in general and the specific disciplines like sucking, early mothering and toilet training in particular have been greatly exaggerated. He proposes, instead, a theory that emphasizes the effect of constitutional factors and the total cultural situation in personality formation, together with postinfantile experience, a formulation that seems eminently reasonable.

Benedict,[5] another anthropologist, has approached the same problem of whether or not early infantile experiences influence personality development by an investigation of the practice of swaddling in certain Eastern European cultures. She found no evidence for the widely held view that restraint of motion, which is an essential feature of swaddling, produces tics or that depriving the infant of finding pleasure in his own body is harmful in later life.

Strange as other customs of child rearing may seem, it is well to keep in mind that, as nearly as one can observe, they have not been psychologically traumatic. There are many ways of bringing up children. It is becoming increasingly clear that the deviations from the principles of child rearing that one has come to accept are less important, so far as their effects on the child are concerned, than the state of mind or the general attitude of the parent toward the child.

This is also the point of view of Dr. Margaret Mead,[6] a member of the group that conducted the research reported by Benedict. She concludes that "it is not possible to make any simple statement, such as that permissive toilet training or long nursing or sudden weaning have a single predictable effect on personality development." Whenever any single practice was followed in the various national groups, a confusing number of contradictions were found. It has become increasingly clear over the last few years, Mead states, that the important thing in child rearing is the quality of the relation between mother and infant, rather than a technic.

The idea that infantile and early childhood experiences have profound and often specific influence on personality development is an unwarranted generalization. The persons who are permanently damaged by improper training procedures are those in whom the unfavorable management has continued to operate over long periods during childhood. There is every reason to believe that the run-of-the-mill errors in child rearing that parents make will be without serious consequences in the large majority of cases.

Adverse Effects of Current Psychiatric Teaching

On the whole the effects of current psychiatric teaching have been to increase parental anxiety, to shake the faith of parents in their own ability to rear children and to undermine parental authority. These are the direct results of such unsubstantiated ideas as that every experience, from the time of birth or even earlier, leaves an indelible impression on the child's future emotional life; that every act of the parents, as it concerns the child, has for him permanent meaning; that a frustration is harmful; and that the process of child development is a delicately balanced and hazardous one, easily deflected and distorted.

In America the influence of these false teachings is widespread. The pleasures of parenthood are tempered by anxieties, uncertainties and feelings of inadequacy and guilt. Pediatricians are only too familiar with the everyday question: "I did so-and-so to my child. Did I make a mistake?" Too often they hear mothers blaming themselves for their children's misbehavior, attributing it to some error in upbringing or to the fact that the mother had a job during the youngster's early years. Little wonder that parents, unsure of themselves and uncertain of the meaning of their behavior, are unable to exert the direction and authority that a child expects from his parents and needs for his best development. Moreover, children sense the parental anxiety and unsureness and take on these feelings themselves. Concentration of attention on the importance of parental affection has led to fear that discipline will jeopardize the parent-child relation. With the use of the developing capabilities and feelings as cues to management, a sound principle has been falsely interpreted as implying that the child should be indulged without limit.

It is to be expected that parents of a neurotic temperament will be more severely affected by current psychiatric teaching than those whose emotional make-up is sturdier. But it would be a mistake to assume that only the emotionally distorted are disturbed in this way. Most of the mothers who are, at first, overly anxious about the problems of child rearing come, with time, to appreciate the hardiness of the human constitution and the strong drive toward normal development and, with their second and subsequent children, lose much of their early anxiety.

Popular psychiatric teaching is not the only reason for the present increase in parental anxiety. Escalona[7] proposes that current attitudes toward children owe their popularity largely to the receptivity of parents, which, in turn, is related to the peculiar circumstances of the present. The strict scheduling and precise formulations of earlier decades reflected a self-confidence and a faith in the future that have been to a large extent dissipated by cur-

rent uncertainties. Until recently, technologic advance was regarded as the means by which the problems of human existence would be solved. It has become evident, however, that technologic advance can also destroy existence. An important consideration is the widespread conviction that man himself, rather than some supernatural force, is responsible for the trend of world affairs and that man can blame only himself for the present political and moral confusion. Other considerations are the decline in the influence of religious teaching and the increase in employment of women outside the home, often accompanied by strong guilt feelings.

Probably the principal shortcoming of currently popular attitudes on child rearing is the failure to emphasize the personality attributes that parents and society at large prize most highly — namely, character. There was a time when professional interest in the child was centered on the physical attributes. It was assumed — tacitly — that, if the child was physically healthy, emotional development would take care of itself. It soon became apparent, however, that, proper though prescriptions may have seemed as far as supplying the physical needs was concerned, the child often resisted. Examples are the difficulties arising from the rigid prescriptions for the care of infants and the frequency of feeding difficulties during the preschool period. Consequently, the concept of child care was broadened to include attention to the emotions. And now, much as before, it is assumed tacitly that character building will somehow proceed satisfactorily.

I do not propose that the task of character building is in the province of the physician, and I should prefer to have it remain where I believe it belongs: in the home, the church and the school. It becomes, however, a matter of concern to the physician when professional attention to emotional development interferes with the inculcation of sterner and nobler personality attributes that are essential for life in a free and gracious society. Emotional development, like physical, is to a large extent innately determined, and most deviations take place only when the environment is grossly abnormal. On the other hand the attributes that make up "character" are determined, in the main, culturally and are taught to the child by the persons about him.

The erroneous ideas that early childhood experiences influence personality development and that specific errors lead to specific behavior deviations later on have led to an overconcern with technics and a blurring of the true objectives. Deprived of the prop of tradition that prescribed in detail the technics of child care, parents concern themselves unnecessarily over nonessentials. For the most part, the psychologic implications of infant rearing are significant so far as they affect the parent-child relations, and these, as the child grows older, influence more and more the personality development of the child.

Experience shows that children thrive best in a home atmosphere where they believe that their parents are sincerely fond of them, where they are accepted for what they are without undue pressure, where discipline is firm and consistent and where character building is fostered by example, by precept and by just reward for proper behavior. Given such a home, it matters little for the psychologic development of the child whether or not he is nurtured at the breast or by bottle, by self-demand or rigid scheduling, or whether toilet training is too early or too late.

It is not my intention to imply that these devices are without value. I believe, however, that their importance has been exaggerated and that harm has thereby been done. During infancy the parents become acquainted with their child, and the parental attitudes are, in the main, set. This is the optimal time for parents to begin to establish a sense of intimacy with the child. The experienced physician uses many devices to foster such a relation — praise of the baby, praise of the mother for her adept handling of the baby, admiration for the family group and so on.

Having mother and child together in the obstetric hospital favors such an intimacy, and this is one of the principal advantages of the rooming-in system. It is, in addition, kinder to let the mother have the baby at her side rather than to make her — and the father — submit to the rigid, artificial restrictions of the "well run" obstetric hospital. Breast feeding, which is encouraged in the rooming-in setup, also favors a closer relation between mother and child and is consequently to be preferred. Similarly, allowing a baby to have as much as he wants at a feeding within reason seems sensible. Training a child when he is developmentally ready — whether for self-feeding, for toilet control or for keeping a promise — is easier on the parent and child and more apt to be successful than premature or delayed training.

The task of bringing up children must be adjusted not only to the individuality of the child but also to the personalities of the parents, their experiences and the culture in which they move as well. It is unwise to try to impose on parents patterns of behavior that are difficult for them to live up to. Individualization is fully as necessary in dealing with the mother as it is with the child. If the physician is convinced that self-regulation is going to make the mother overly anxious or otherwise unhappy, more or less specific directions should be given. An approach that she finds uncongenial will not only disturb her emotionally; it will make her task more difficult and will probably create unnecessary tensions in the child. For one reason or

another many mothers find the decisions implicit in "self-demand" feeding a source of great anxiety. To them specific directions are a great comfort.

The principal aim in child rearing is character building. It is the pediatrician's task to foster a wholesome atmosphere in the home, to bolster parental self-confidence and to see to it that parents are not deflected from this central objective by false teachings and unsubstantiated rationalizations.

What I have said here may have given the impression that I am skeptical of clinical child psychology and psychiatry and of its achievements. This is not my intention. Solid contributions, faithfully documented and critically evaluated, have been made all along the line. In child psychology one can point to the monumental labors of Arnold Gesell and his group of co-workers as well as to a host of others. Much of the work done recently is summarized in convenient form in Carmichael's *Manual of Child Psychology*. The studies have laid the groundwork for a clearer understanding of psychologic development and for a rational approach to the management of deviations.

In child psychiatry recent years have witnessed the clarification of a number of syndromes — schizophrenia, infantile autism, organic brain disease, reading disability and enuresis. There is a better understanding of the psychologic aspects of diseases like asthma, skin eruptions, obesity, and ulcerative colitis, as well as many others. An appreciation of the mental attitudes of patients with conditions such as rheumatic fever, tuberculosis, deafness and blindness should make their management more comprehensive, more effective and, at the same time, more humane. An appreciation of the adverse psychologic effects of the hospital on the infant has led to an entire change in the management of hospital baby wards.

Unfortunately, the solid contributions are often obscured by the exaggerated claims of the overzealous.

It should be remembered that children are hardy creatures, and that they will take a great deal of pushing around without being harmed. The urge toward normal growth and development is strong. It is the pediatrician's oldest and most powerful ally. Those who have had an opportunity to observe children over a period of years have been repeatedly delighted to see children who, for one reason or another, seemed headed for disaster overcome their difficulties and eventually function as healthy, happy adults.

This important concept is implied in a poignant little couplet attributed to one of Nature's unfortunate failures. In the cemetery at Chiswick, just outside London, stands the tiny tombstone of a baby who died at the age of nine days. On it are inscribed the following lines:

> If I was so soon to be done for
> What was I ever begun for?

During the past twenty-five years sharp changes have occurred in what may be called "official" attitudes toward child rearing — from the rigid, stern, strict scheduling of the early decades of this century to the highly permissive teachings of the late thirties and forties. I believe that pediatricians will continue to err in the same way, going from one extreme to the other, from one fad to another, as long as they center attention on the technics of child rearing and fail to comprehend the essence and principal aim of child rearing, which is character building. The particular qualities that parents would inculcate in their children are, to a large extent, individual and personal. Some parents would emphasize in their children integrity of purpose, others humility, others kindness and generosity, and still others force of character and initiative. This is the parents' privilege — indeed, it is their duty.

The technics of child rearing are also largely individual. It has been my thesis, for many years, that one does best by following the cues offered by nature. Only when nature breaks down — as in severe illness — is one justified in applying drastic methods. Some parents will rear their children principally by kindness and gentle persuasion; others, equally affectionate and interested, will resort to sterner measures. How a parent brings up his children is, to a large extent, an expression of his own personality. It is the right of parents to bring up their children as they see fit. But this right — like every other right — implies an obligation: the obligation to rear children in accordance with the noble ideals of a free society.

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MEDICAL PROGRESS

PHARMACOLOGIC ASPECTS OF ADRENOCORTICAL STEROIDS AND ACTH IN MAN*

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THE importance of the adrenocortical steroids as essential mediators of metabolic processes is well established. In the treatment of adrenocortical insufficiency these hormones are capable of restoring severely ill patients to a state of health that is remarkably near normal. In the wider field of inflammatory diseases their action is no less dramatic, although the indications for their use and their ultimate place in the therapeutic armamentarium are not yet clearly defined. Experience has emphasized the necessity for exercising unusual care in initiating or terminating a therapeutic trial with these agents. Regardless of the extent to which they may eventually be employed in the everyday practice of medicine, the necessity for understanding as clearly as possible their mode of action in the human body remains. This review is presented, therefore, in the hope that a reassessment of the more important pharmacologic aspects of the action of the adrenocortical hormones may prove useful to the practicing physician. The structure of the C-21 adrenal steroids is shown in Figure 1.

11-DESOXYCORTICOSTERONE

The first adrenal steroid to be synthesized was 11-desoxycorticosterone (Fig. 2).[1] In this instance, the synthesis of a steroid hormone was accomplished prior to its identification and isolation from adrenal-gland extracts.[2] The important physiologic processes that this hormone controls are well established. Whether or not a hormone of this exact chemical composition is secreted by the normal human adrenal gland has been open to serious question. Because of its marked potency one might expect to find only traces of desoxycorticosterone in adrenal extracts or perfusates. It has been considered that the virtual elimination of sodium from the urine of normal subjects treated with ACTH probably indicated the secretion of an adrenal steroid more salt-retaining than either the 11 or 11,17-oxygenated steroids. However, recent experiments[3] have shown that the intravenous infusion of hydrocortisone (Compound F) in a normal subject at the rate of 12 mg.

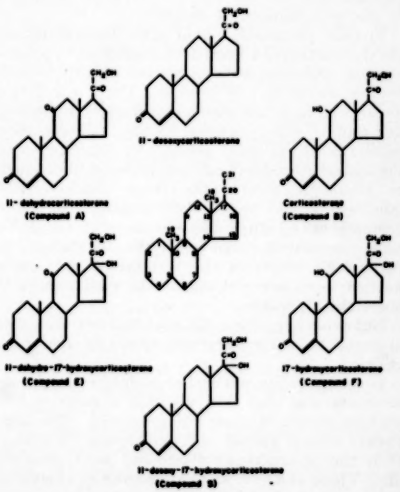

FIGURE 1. *Structure of C-21 Adrenal Steroids.*

per hour is capable of inducing profound sodium retention; hence the occurrence of a marked reduction in the sodium excretion after intensive ACTH stimulation does not necessarily require the secretion of 11-desoxycorticosterone-like steroids.

On the other hand, the probability that the adrenal glands secrete desoxycorticosterone is suggested by the experiments of Hechter et al.,[4] who have detected 11-desoxycorticosterone in blood

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after perfusion of isolated beef adrenal glands. Recent experiments of Simpson et al.[8] have demonstrated that a new and highly potent electrolyte-regulating compound is present in adrenal-gland extracts and in the adrenal venous blood of laboratory animals. This compound was found to be distinct from cortisone, hydrocortisone, corticosterone and 11-desoxycorticosterone, was much more potent in its salt-retaining capacity than any of these agents and appeared to be responsible for most of the electrolyte regulating activity of the original extract. Finally, it should be remembered that the amorphous fraction remaining after the preparation of adrenocortical aqueous extracts contains highly effective, and as yet unidentified, electrolyte-regulating substances.[6] Although under circumstances of maximal adrenocortical stimulation it is possible that electrolyte regulation could be mediated by the quantity of Compound-F-like substances secreted, in all likelihood under normal circumstances electrolyte regulation is effected through the action of more potent salt-retaining substances. It must be admitted that whereas the exact status of desoxycorticosterone as a natural mineralocorticoid is still uncertain, it remains the most potent steroid available today for the control of sodium and potassium urinary excretion.

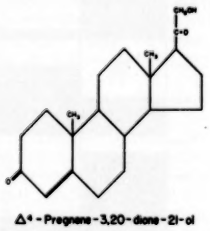


FIGURE 2. *Structure of 11-Desoxycorticosterone.*

Physiologic Actions

Desoxycorticosterone, when administered in adequate dosage to normal subjects, as well as to patients with adrenocortical insufficiency, produces definite changes in electrolyte and water balance, as regulated by the kidneys, sweat glands, salivary glands, gastrointestinal tract and, in all probability, body cells in general. As might be anticipated, these effects are demonstrated much more readily in patients with Addison's disease than in subjects with intact adrenal glands.

Kidney. The renal effects of desoxycorticosterone in man consist of the retention of sodium, chloride and water and an increased excretion of potassium.[7] Although changes in the urinary excretion of calcium and phosphorus may occur, the effects on total balance are variable and usually of a minor degree. In patients with adrenocortical insufficiency, desoxycorticosterone produces, as a direct result of the restoration of electrolyte and water balance, an expansion of plasma and extracellular fluid volumes, a gain in body weight and a rise in blood pressure.[8, 9] In addition, renal plasma flow, glomerular filtration rate and the clearance of urea and endogenous creatinine are enhanced. The studies of Pitts[10] suggest that these changes in renal hemodynamics are secondary to the restoration of total body electrolyte and water content resulting from the primary action of the hormone on the renal tubule. Thus, it appears probable that the primary effect of desoxycorticosterone on kidney function is the enhancement of sodium reabsorption and of potassium elimination by the renal tubules. Indeed, patients with advanced kidney disease characterized by enormous losses of urinary sodium and chloride ("salt-losing nephritis")[11] are unable to respond to desoxycorticosterone administration with either sodium retention or an increased output of potassium.

The mechanisms by which desoxycorticosterone influences the regulation of electrolyte excretion by the renal tubules have been investigated by Pitts.[12] These studies, carried out in adrenalectomized dogs, indicate that adrenocortical steroids are capable of regulating the reabsorption of approximately 2 per cent of the total tubular load of filtered sodium. It appears likely, on the basis of the response engendered by the stress of moderate acid loading (for example, with ammonium chloride), that desoxycorticosterone influences the tubular exchange of sodium, potassium and hydrogen ions. However, the modifying influence exerted by desoxycorticosterone upon the renal actions of mercurial diuretics and Pitressin suggests that the hormonal action on electrolyte excretion is not confined to its effects on the ion-exchange mechanisms. A direct effect on the tubular processes responsible for ammonia secretion may also occur.[13] The locus of these actions is considered to be the distal tubules.

Studies carried out in normal human subjects show a definite effect on the renal excretion of electrolytes within two to four hours of the intramuscular,[14] as well as intravenous,[3] administration of desoxycorticosterone. It is of interest that the administration of desoxycorticosterone acetate to human subjects during the rigid restriction of sodium intake produces little or no rise in the urinary excretion of potassium and has no effect on the external exchange and internal distribution of water.[15, 16] These results suggest the existence of a renal mechanism that controls the excretion of both sodium and potassium and is subject to the influence of desoxycorticosterone, as suggested by Pitts[12]; furthermore,

it is apparent that the effect of the hormone on potassium elimination is conditioned by the degree of concurrent sodium retention.

In contrast to patients with Addison's disease, in whom the effects described above are ordinarily obtained at a dosage level of 1 to 3 mg. per day, normal subjects usually require the administration of considerably larger quantities of desoxycorticosterone, 10 mg. per day or more, to elicit comparable changes. Moreover, the prolonged administration of hormone in normal subjects is characteristically followed by an escape from its effects on sodium and potassium excretion.[16] A return of normal potassium balance ordinarily follows that of sodium. It is of interest that the prolonged administration of large amounts of desoxycorticosterone acetate to dogs may produce a marked increase in water intake and urine output (diabetes-insipidus-like syndrome).[17] This has been attributed to excess sodium retention and consequent thirst although alternative explanations have been presented. A similar, although less marked, effect has been described in human subjects treated for prolonged periods with large quantities of desoxycorticosterone.[18]

Sweat. Conn and his associates[19] have shown that the concentration of sodium and chloride in sweat, in certain circumstances, can be correlated with the level of adrenocortical activity. Desoxycorticosterone produces a marked fall in sodium and chloride concentration and a rise in potassium concentration in the normal subject as well as in the patient with Addison's disease. In contrast to the effects observed on the renal excretion of electrolytes, however, continued administration of the hormone to normal subjects is not accompanied by an "escape" from sodium retention and potassium loss.

TABLE 1. *Effect of Desoxycorticosterone Acetate on the Salivary Ratio of Sodium to Potassium.*

TREATMENT	RATIO OF SODIUM TO POTASSIUM
0	1.1
0	0.95
0	1.0
0	0.95
DCA, 15 mg. intramuscularly	0.73

Saliva. Changes in the electrolyte composition of the saliva follow the pattern in sweat — that is, desoxycorticosterone causes a decrease in sodium and chloride concentration and a rise in potassium concentration. Frawley[20] has demonstrated the usefulness of determining the ratio of sodium to potassium in saliva as a measure of activity of the adrenal salt-retaining hormones. The effect of desoxycorticosterone upon the ratio in a normal subject is shown in Table 1.

Gastrointestinal tract. The adrenal hormones probably affect the intestinal secretions in a manner comparable with the effect on the salivary and sweat glands. Since most of the electrolytes secreted into the intestinal tract are reabsorbed, however, there is ordinarily little opportunity to observe this effect. Berger et al.[21] raised the sodium content of the stool by administering a cation-exchange resin to 3 patients and then were able to demonstrate a decrease in fecal sodium content after desoxycorticosterone acetate administration. The quantity of desoxycorticosterone employed was not stated. We have carried out a similar study in a patient with Addison's disease and have demonstrated a definite measure of protection with desoxycorticosterone acetate, 20 mg. daily injected intramuscularly, against the increased loss of sodium in the bowel caused by the oral administration of a cation-exchange resin[22] (Fig. 3). It is possible that the gastrointestinal upsets observed so frequently in patients with untreated Addison's disease are intensified by a failure to reabsorb sodium and chloride effectively from the lumen of the bowel.

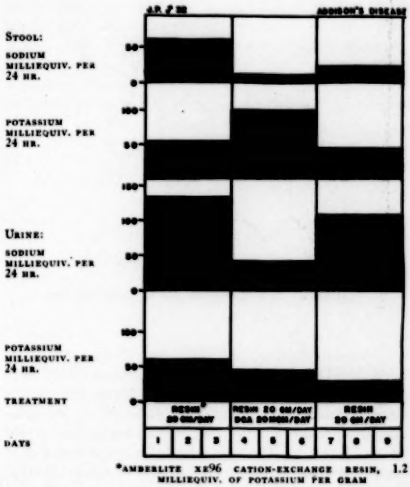

A.P. ♂ 38
ADDISON'S DISEASE
STOOL:
SODIUM MILLIEQUIV. PER 24 HR.
POTASSIUM MILLIEQUIV. PER 24 HR.
URINE:
SODIUM MILLIEQUIV. PER 24 HR.
POTASSIUM MILLIEQUIV. PER 24 HR.
TREATMENT
RESIN* 20 GM./DAY
RESIN 20 GM./DAY DCA 20 MGS./DAY
RESIN 20 GM./DAY
DAYS
1 2 3 4 5 6 7 8 9
*AMBERLITE XE96 CATION-EXCHANGE RESIN, 1.2 MILLIEQUIV. OF POTASSIUM PER GRAM

FIGURE 3. *Excretion of Sodium and Potassium in a Patient with Addison's Disease.*

The patient was on a constant diet — 240 milliequiv. of sodium and 72 milliequiv. of potassium. Stools and urine were collected in three-day pools, and the values for sodium and potassium represent average daily excretion.

Body cells. During the administration of desoxycorticosterone to normal subjects, or to patients exhibiting overt signs of adrenocortical insufficiency, the expansion of extracellular fluid volume may

well exceed the change in external water balance, indicating a shift of water from intracellular to extracellular space.[23-25] A significant elevation of intracellular sodium and a decrease in intracellular potassium have also been frequently demonstrated during desoxycorticosterone administration to animals[26] and man.[14, 27] It appears probable that these changes in intracellular composition are largely dependent upon alterations in electrolyte balance produced by intensive renal tubular sodium retention and potassium loss.

However, it has long been recognized that desoxycorticosterone may exert an effect on intracellular electrolytes and water independent of its effect on renal tubules. Consistent with this is the fact that Woodbury[28] has succeeded in demonstrating a change in the tissue content of sodium in the nephrectomized rat receiving desoxycorticosterone acetate.

Recent studies by Luft,[29] in which simultaneous measurements of sodium balance and total Na24 space were carried out in patients with intact adrenal glands receiving large doses of desoxycorticosterone acetate over prolonged periods, provide further evidence for extrarenal actions of this steroid. Although the initial period of marked sodium retention was followed in all cases by an escape to a state of normal balance and even negative balance during continued desoxycorticosterone administration, the distribution space of radiosodium steadily enlarged. The lack of correlation between external balance and internal distribution must signify a direct effect of the hormone on sodium stores independent of its action on sodium excretion.

Other actions. Sayers[30] has demonstrated a weak action of desoxycorticosterone acetate in inhibiting pituitary secretion of ACTH. This effect is not potent enough to be of pharmacologic significance in man, in the dosage usually employed in the regulation of Addison's disease — that is, 2 to 5 mg. daily. Although improved food intake and electrolyte regulation are the principal factors responsible for the alterations observed in carbohydrate metabolism in most patients with Addison's disease, all available evidence points to the conclusion that desoxycorticosterone exhibits a minimal direct effect on carbohydrate metabolism. The administration of desoxycorticosterone does not induce eosinopenia, and no cortisone-like effect on inflammatory and allergic phenomena is observed.

Patients with Addison's disease on long-continued desoxycorticosterone maintenance therapy, despite an improved sense of well-being and capacity to work, usually exhibit one or all of the following metabolic abnormalities: incapacity to tolerate prolonged fasting without hypoglycemic manifestations; abnormal response to water load; and persistence of the abnormal electroencephalographic pattern.

Although it is well recognized the desoxycorticosterone can produce a progestational endometrium in estrogen-treated ovariectomized or immature animals,[31] comparable effects have not been demonstrated in human subjects.

Toxicity

The undesirable side effects that may follow desoxycorticosterone overdosage are the direct result of an accentuation of the metabolic effect obtained with physiologic quantities of the hormone. These include hypernatremia, hypokaliemia, edema, hypertension and cardiac enlargement.[24] With intensive sodium retention and potassium depletion a significant intracellular exchange of sodium for potassium may occur. Advanced intracellular potassium loss may eventually result in serious muscular weakness and even paralysis; under these conditions, morphologic lesions in cardiac muscle may be found.[32] These changes can be effectively minimized by a restriction of sodium and chloride intake and the administration of supplementary potassium.

In view of the potential importance of the adrenal cortex in the maintenance of experimental and essential hypertension[33, 34] considerable interest has centered upon the capacity of excessive quantities of desoxycorticosterone acetate to provoke hypertension in patients with Addison's disease.[35] Furthermore, it has been noted that blood pressure may be restored to abnormally high levels by the administration of desoxycorticosterone to normotensive patients with Addison's disease who were afflicted with essential hypertension prior to the development of adrenal insufficiency.[36] Although the administration of desoxycorticosterone to patients with essential hypertension[34] has been reported to produce a significant rise in blood pressure, this effect is quite unusual in normal subjects.[35] The observation that prolonged administration of large quantities of desoxycorticosterone acetate to patients with "salt-losing nephritis" causes no rise in blood pressure, and, in the absence of a sufficient intake of sodium chloride, may be accompanied by actual hypotension, indicates that this action of the hormone is in all likelihood dependent upon the intact kidney, but does not distinguish between an effect on sodium retention and a possible influence upon the renal production of vasopressor substances.

Absorption

Desoxycorticosterone acetate is absorbed readily by the intramuscular or subcutaneous route and also by the mucous membranes of the mouth. It differs from other adrenal steroids such as corticosterone, cortisone and hydrocortisone in being relatively ineffective when administered orally. Kuizenga and Nelson[37] have shown in rats that desoxycorticosterone acetate is one thirty-fifth as effective orally as parenterally and that it is destroyed locally in the gastrointestinal tract. This finding is in agreement with clinical experience.[38]

Investigations of the percutaneous and rectal routes of administration in patients with Addison's disease demonstrated absorption to be poor.

Intermediary Metabolism and Excretion

Little is known of the metabolic processes involved in the degradation and transformation of desoxycorticosterone. Hechter et al.[4] reported that the perfusion of this hormone through beef adrenal glands gave rise to the formation of corticosterone (Compound B). Recent studies by Schneider[39] on the incubation of desoxycorticosterone with surviving rat-liver slices have demonstrated a rapid disappearance of the conjugated, unsaturated system (3-keto-delta-4-structure). Four allopregnane derivatives, three of which possess a hydroxyl group at carbon-3, were isolated. It is of interest that bioassay of the ketonic fraction indicated that approximately 3 per cent of the incubated desoxycorticosterone had been converted to androgenic material.

Although none of the metabolites isolated by Schneider have been shown to be excretory products of desoxycorticosterone, there is sufficient evidence that the hormone is excreted, at least in part, as pregnanediol. Horwitt et al.[40] have demonstrated pregnanediol excretion after the oral administration of desoxycorticosterone acetate to 2 male and 1 female patient with Addison's disease and to 1 male subject with hypogonadism. Similarly, Cuyler et al.[41] were able to demonstrate this transformation in healthy men.

The administration of desoxycorticosterone acetate to patients with Addison's disease does not, in the dosages ordinarily employed for clinical management, give rise to an increased excretion of urinary 17-ketosteroids. However, studies on ovariectomized and ovariectomized-adrenalectomized primates have demonstrated the conversion of desoxycorticosterone to 17-ketosteroids.[42]

Preparations

It has long been recognized that the metabolic activity of steroid hormones can be significantly modified by esterification and by the physical state in which they are administered. Miescher et al.[31] originally demonstrated significant differences in the duration of effects exerted by the acetate, palmitate and butyrate esters of desoxycorticosterone in oil solution. For many years, however, the acetate of desoxycorticosterone has generally been employed for clinical use. A significant advance in the administration of steroid hormones was achieved by the formulation, by Deanesly and Parkes,[43] of estrogenic and androgenic hormone tablets for subcutaneous implantation. Thorn et al.[44] subsequently standardized the maintenance treatment of patients with Addison's disease by the subcutaneous implantation of desoxycorticosterone acetate pellets. In addition, both the intravenous and intraoral routes have been utilized for the administration of this hormone to patients with adrenocortical insufficiency.

Six preparations of desoxycorticosterone are presently available for clinical use: desoxycorticosterone acetate in sesame or peanut oil, for intramuscular injection; desoxycorticosterone acetate pellets, for subcutaneous implantation; desoxycorticosterone in propylene glycol, for sublingual administration; desoxycorticosterone acetate buccalets, for intraoral absorption; a microcrystalline aqueous suspension of desoxycorticosterone trimethyl acetate, for intramuscular injection; and an aqueous solution of desoxycorticosterone glucoside designed for intravenous infusion.

Desoxycorticosterone acetate in oil. After its initial synthesis and isolation, the acetate ester of desoxycorticosterone was promptly shown to be of therapeutic value in the management of both acute and chronic adrenocortical insufficiency.[45, 46] Desoxycorticosterone acetate in sesame oil, administered by deep intramuscular injection, was thereafter widely employed for the maintenance therapy of patients with Addison's disease and, subsequently, for the standardization of daily hormone requirement prior to the implantation of pellets for long-term treatment. The preparation is ordinarily administered once daily since the effects of a single intramuscular dose endure for approximately twenty-four hours. The average daily dose used in the treatment of patients with Addison's disease is 1 to 3 mg. a day.[47] Larger doses of 5 mg. or more may be required in unusual patients and in adrenal crisis.

Desoxycorticosterone acetate pellets. The maintenance therapy of patients with Addison's disease by the subcutaneous implantation of desoxycorticosterone acetate pellets offers certain distinct advantages: the provision of a more constant rate of hormone absorption; reduction of the total hormone requirement, owing to the efficiency of utilization resulting from continuous absorption; and the avoidance of daily intramuscular injections. During the past decade the administration of desoxycorticosterone acetate by this technic has without doubt constituted the mainstay of substitution therapy in the majority of patients with chronic adrenocortical insufficiency, and has been responsible in no small part for a significant reduction in the mortality of this disease.[48]

Two pellet preparations are currently available, one containing approximately 125 mg., and the other 75 mg. of hormone. Pellets containing 125 mg. of desoxycorticosterone acetate are absorbed at a rate of approximately 0.3 to 0.4 mg. per day, which is equivalent, in terms of metabolic effect, to the daily intramuscular injection of approximately 0.5 mg. of the hormone in oil solution.[49] It is apparent that the continuous absorption of hormone provided by subcutaneous pellets is approximately 25 per cent more efficient than that resulting from inter-

mittent intramuscular injection. One pellet, therefore, may be considered equivalent to a daily dose of 0.1 cc. of the standard preparations of desoxycorticosterone acetate in oil. Pellets containing 75 mg. of hormone are absorbed at a rate of approximately 0.24 mg. a day[50] and are equivalent to approximately 0.05 cc. of the oil solution injected daily.

The number of pellets required for optimal maintenance therapy is established on the basis of the daily requirement of desoxycorticosterone acetate in oil administered by intramuscular injection. The duration of effective electrolyte control achieved during substitution therapy by pellet implantation is approximately eight to twelve months. This method of hormone administration therefore produces the longest therapeutic action of the preparations of desoxycorticosterone currently available for clinical use. The technic of pellet implantation has been adequately described elsewhere.[48]

Sublingual and intraoral preparations of desoxycorticosterone acetate. The administration of desoxycorticosterone acetate by the sublingual and intraoral routes has been advocated by Anderson et al.[50] The sublingual preparation was administered in droplet form, the hormone being dissolved in propylene glycol and alcohol. Early studies with this preparation[28] demonstrated that approximately 5 mg. of the hormone administered sublingually in divided doses throughout the day was required to produce a metabolic effect equivalent to that resulting from the daily absorption of 1 mg. of desoxycorticosterone acetate from subcutaneous pellets. The necessity for frequent administration, the objectionable taste experienced by some patients and a tendency to precipitate on cooling or exposure to air have largely resulted in the replacement of sublingual drops by the intraoral tablet or buccalet, which, available as hard compressed tablets containing 2 mg. of desoxycorticosterone acetate in a propylene glycol-wax base, is placed either in the buccal pouch or beneath the tongue for direct absorption through the oral mucous membrane. The average hormone dose reported by Anderson et al.[51] was 4.8 mg. a day, ordinarily administered in divided doses. It is to be emphasized that the administration of desoxycorticosterone acetate by this route does not provide adequate treatment for patients in adrenal crisis.

Microcrystalline suspension of desoxycorticosterone trimethylacetate. Recently, the trimethylacetate ester of desoxycorticosterone originally prepared by Wieland et al.,[52] has been demonstrated to produce a protracted metabolic effect in man[53] and animals[54, 55] after the intramuscular administration of a single dose. An extensive clinical trial in patients with Addison's disease has confirmed these observations and established the usefulness of this preparation in substitution therapy.[56] The preparation employed, soon to be available for general use, is a microcrystalline suspension of desoxycorticosterone trimethylacetate in isotonic saline solution, containing methyl cellulose and Tween 20 as suspending agents. An average crystal size of 50 microns ensures a freely injectable suspension. Balance studies have revealed maximal sodium and chloride retention within forty-eight hours of injection (Fig. 4). The average period of effective electrolyte regulation resulting from a single intramuscular injection in patients with adrenocortical insufficiency is five or six weeks. Approximately a thirtieth to a fiftieth of the injected dose is absorbed daily. Therefore, the administration of a single 30-mg. dose provides a daily absorption of approximately 0.6 to 0.8 mg. The injections are conveniently administered at monthly intervals to ensure sufficient overlap of metabolic effects to avert all evidences of inadequate hormonal control. The advantages of this technic of desoxycorticosterone administration are as follows: infrequent injections; avoidance of the minor surgical procedure involved in pellet implantation; flexibility of dosage schedules; and constancy of control, especially in comparison to the terminal period of pellet therapy, during which the symptoms of adrenal insufficiency appear comparatively often.

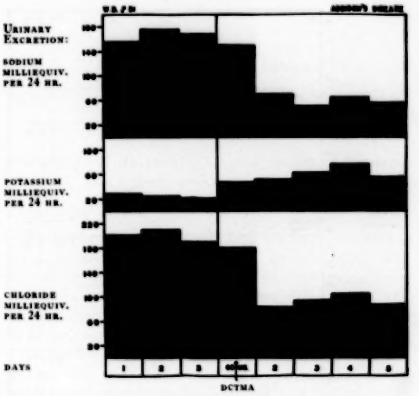


FIGURE 4. *Effect of Desoxycorticosterone Trimethylacetate on Electrolyte Excretion.*

The patient was on a constant diet that included 146 milliequiv. of sodium and 64 milliequiv. of potassium. The trimethyl acetate of desoxycorticosterone was given as a single intramuscular injection.

Desoxycorticosterone glucoside. Desoxycorticosterone glucoside, originally prepared by Miescher et al.,[57] is considerably more water-soluble than

either free desoxycorticosterone or the acetate ester. The material is available as a 1 per cent solution in 10 per cent glucose, containing 10 per cent acetamide for stabilization, and has been chiefly employed for intravenous administration. Comparative studies in animals have demonstrated that the water-soluble glucoside produces a more rapid onset of action and a more transient effect than the oil solution of desoxycorticosterone acetate.[58] Swingle[59] has found that the intravenous administration of desoxycorticosterone glucoside in doses of 300 mg. is capable of reviving adrenalectomized dogs from severe adrenal insufficiency, even when no supplementary therapy is employed.

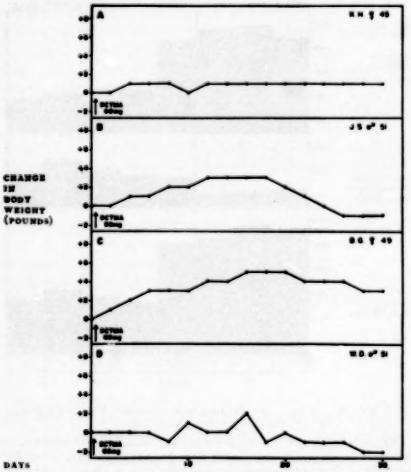


FIGURE 5. *Weight Curves in Patients with Addison's Disease Treated with Desoxycorticosterone Trimethyl Acetate.*
A = *no weight change — satisfactory dose.*
B = *typical weight chart, with slight weight gain in the middle of the period — satisfactory dose.*
C = *excessive weight gain, with edema — overdosage.*
D = *weight loss toward the end of the period, indicating underdosage.*

Administration of this preparation to human subjects by intramuscular injection[60] and intravenous infusion[61] resulted in sodium and chloride retention; in addition, an increase in water excretion and a decrease in the tubular reabsorption of glucose during the period of hormone infusion have been described. Desoxycorticosterone glucoside has been little used in this country in the treatment of adrenal crisis. Foreign reports[62] indicate, however, that the intravenous administration of 100 to 300 mg. of the glucoside preparation is beneficial. In our experience the effect of these large doses on electrolyte excretion is not significantly greater than that obtained from the daily intramuscular injection of 15 to 20 mg. of desoxycorticosterone acetate in oil.

Clinical Uses of Desoxycorticosterone

The value of desoxycorticosterone in the treatment of Addison's disease is well established. With measurements of body weight, hematocrit, blood pressure and heart size as guides to dosage, the optimal hormone requirement is determined by the daily intramuscular injection of desoxycorticosterone acetate in oil. When dosage has been firmly established at a constant level treatment may be continued with a long-acting desoxycorticosterone preparation.

When subcutaneous pellets are employed for long-term maintenance therapy the following dosage equivalents may be employed: for each 0.5 mg. of desoxycorticosterone acetate in oil injected daily, 1 pellet of 125 mg. may be substituted; alternatively, for 0.3 mg. of the oil solution injected daily, 1 75-mg. pellet may be implanted. Ordinarily, when more than 4 pellets are required, 1 less than the calculated number should be employed to avoid overdosage. The number of pellets implanted in a series of 180 patients with Addison's disease seen in this clinic ranged from 1 to 8 per patient; the average requirement varied between 2 and 4 pellets per implantation.

The alternative method of maintenance treatment is the intramuscular injection of desoxycorticosterone trimethylacetate. Dosage is determined in the same manner described for pellet implantation, and for each milligram of desoxycorticosterone acetate injected daily, 30 mg. of the microcrystalline suspension is administered at approximately thirty-day intervals. Although the quantity of hormone absorbed each day from the depot of long-acting material is actually somewhat less than that provided by daily injection of desoxycorticosterone acetate in oil, the efficiency of constant hormone absorption enhances the ultimate metabolic effect derived from the trimethylacetate ester in the same manner described for subcutaneous pellets. Dosages employed in a series of 60 patients with Addison's disease recently treated with this preparation ranged from 15 to 90 mg. a month, with an average requirement between 30 and 60 mg. One may most easily determine the adequacy of the dose by following the patient's weight (Fig. 5). In our opinion, this technic of desoxycorticosterone administration currently constitutes the method of choice for long-term maintenance therapy.

Desoxycorticosterone, along with cortisone, has also been employed as replacement therapy in patients who have undergone bilateral complete adrenalectomy for hypertension, or for reactivated

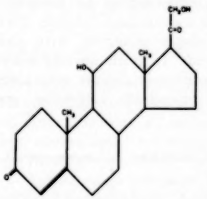
carcinoma of the prostate with metastases.[63] In the former group, an attempt is made to obtain adequate regulation with cortisone and supplementary salt. In some cases, however, the administration of minimal quantities of desoxycorticosterone is essential for the maintenance of electrolyte balance. Whereas from a theoretical point of view desoxycorticosterone therapy is contraindicated in the treatment of patients with hypertensive vascular disease after complete adrenalectomy, this is not true in the management of post-adrenalectomy prostatic cancer since the quantities of desoxycorticosterone employed in the clinical regulation of electrolyte metabolism lead to no detectable increase in the urinary excretion of substances with androgenic activity.

Advantage has been taken of certain of the physiologic actions of desoxycorticosterone in attempts to modify other clinical conditions. The observation that the administration of desoxycorticosterone acetate to normal rats lowers the threshold of response to electroconvulsive therapy[64] has led to the use of this hormone in patients with epilepsy.[65, 66] In some cases a decrease in the frequency and severity of attacks has been noted. Because of certain striking similarities between adrenal crisis and traumatic shock,[67] desoxycorticosterone has undergone extensive clinical and experimental trials in the treatment of the latter syndrome. The results obtained have been conflicting and exceedingly variable.[68] In view of its potential effects on blood pressure, the hormone has been tried as an adjunct in the therapy of patients with syncopal attacks associated with orthostatic hypotension. Continued treatment has resulted in an appreciable rise in both systolic and diastolic blood-pressure levels and a definite amelioration of the syncopal episodes, although a measurable fall in pressure still occurred in the upright position.[22] Because of possible extrarenal effects on the internal distribution of electrolytes, desoxycorticosterone has been administered to hyperkaliemic patients with lower-nephron nephrosis without demonstrable benefit.[69] In the light of recent studies on the regulatory effect of adrenal hormones on gastrointestinal absorption of electrolytes, the possibility of employing desoxycorticosterone in patients with diarrheal diseases should be explored.

Experience to date indicates that desoxycorticosterone is ineffective in the treatment of diseases associated with inflammatory or allergic reactions.

Corticosterone (Compound B)

The presence of corticosterone, or Compound "B" of Kendall (Fig. 6), in relatively high concentration in adrenocortical extracts has long been recognized.[70, 71] Recently, its significance has been emphasized by the studies of Hechter et al.,[4] who have shown that corticosterone and 17-hydroxycorticosterone (hydrocortisone) are the principal steroid substances obtained by perfusion of the isolated bovine adrenal gland with ACTH. The synthesis of corticosterone from a pregnanediol derivative has been achieved,[72] and sufficient material has been made available for study to allow a preliminary



Δ⁴-Pregnene-3,20-dione-11,21-diol

Figure 6. *Chemical Structure of Corticosterone (Compound B).*

evaluation of its clinical as well as its physiologic effects.

Physiologic Actions

As might be anticipated from its chemical structure, corticosterone possesses qualitatively the electrolyte-regulating activity of desoxycorticosterone as well as some of the potentialities of the carbohydrate-regulating hormones (cortisone and hydrocortisone).

In 1940 Thorn et al.[73] gave by intramuscular injection 85 mg. of corticosterone, isolated from adrenocortical extract by Kendall, to a patient with Addison's disease and noted an increase in fasting blood sugar, a depression in nonprotein respiratory quotient and increased resistance to hypoglycemia. In the same year Ferrebee and his co-workers[74] reported little significant effect on either carbohydrate metabolism or electrolyte excretion in a patient with Addison's disease who was given 90 mg. of corticosterone; however, the steroid was given in divided doses over a five-day period, concomitantly with the continued administration of a maintenance dose of desoxycorticosterone acetate.

Only recently, with more liberal supplies of corticosterone available, has further study been possible. In 1951 Conn and his collaborators[75, 76] reported their studies on corticosterone given to normal subjects and to patients with Addison's disease. They were able to demonstrate quite marked sodium-retaining properties: in Addison's disease the daily injection of 25 mg. of the steroid produced sodium retention more marked than that induced by the combined intramuscular administration of 20 mg. of cortisone acetate and 2 mg. of desoxycorticosterone acetate daily; similarly, in a normal subject 200 mg. of corticosterone proved more effective than an equivalent dose of cortisone

acetate. The renal excretion of potassium was increased in patients with Addison's disease and in 1 of 2 normal subjects studied. The associated increase in body weight and decrease in hematocrit were similar to the changes seen with sodium retention induced by desoxycorticosterone. During continued administration to normal subjects an "escape" from sodium and chloride retention similar to that frequently observed with desoxycorticosterone occurred. In both normal subjects and patients with Addison's disease corticosterone led to decreased carbohydrate tolerance, greater resistance to insulin and elevation of fasting blood sugar. As with the electrolyte changes, much larger doses were required to produce these phenomena in normal subjects than in patients with Addison's disease. Furthermore, the effects on carbohydrate metabolism were considerably less striking than those on electrolyte metabolism.

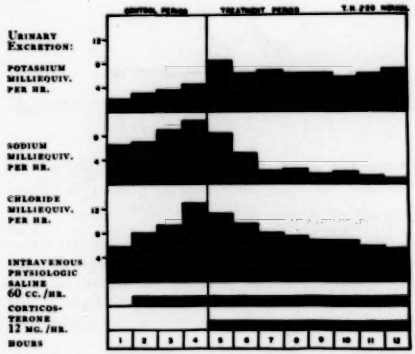


FIGURE 7. *Effects of Intravenous Injection of Corticosterone on Electrolyte Excretion.*
The patient was fasting throughout the experiment.

Our findings in normal subjects, in patients previously subjected to bilateral complete adrenalectomy and in patients with Addison's disease treated with corticosterone are similar to those of Conn et al. and may be summarized as follows:

Desoxycorticosterone effects. The effects of corticosterone on the renal excretion of electrolytes are well illustrated in Figure 7. It is apparent that the intravenous administration of corticosterone (free alcohol) to a normal subject at a rate of 12 mg. per hour over an eight-hour period resulted in marked sodium and chloride retention, with increased potassium excretion. The changes in sodium and potassium excretion became evident within an hour or two of the beginning of hormone infusion, were approximately simultaneous in onset and rapidly attained a maximal level.

The intramuscular administration of corticosterone to patients with adrenocortical insufficiency in doses of approximately 50 mg. a day causes retention of urinary sodium and chloride, promotes urinary potassium excretion and lowers the ratio of sodium to potassium in saliva. These effects appear to be approximately equal to those produced by the daily injection of 1 or 2 mg. of desoxycorticosterone acetate. It is evident that, milligram for milligram, corticosterone is more potent than cortisone in the regulation of electrolyte excretion. Although these actions of corticosterone are more pronounced with intramuscular injection than with oral administration, Figure 8 demonstrates that significant changes in electrolyte excretion can be produced by large doses of the hormone given by mouth.

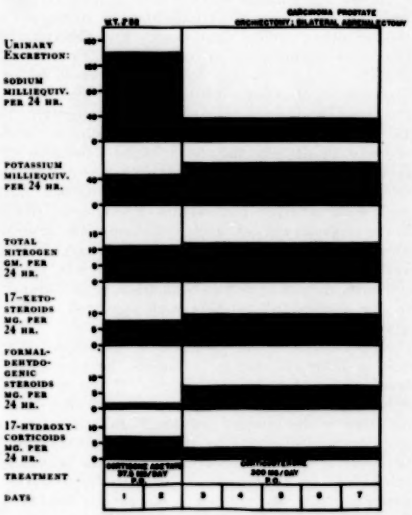


FIGURE 8. *Metabolic Studies on the Effect of the Oral Administration of Corticosterone.*
The patient was on a constant diet (sodium, 141 milliequiv., and potassium, 84 milliequiv.). All values shown represent mean daily excretions. (The increase in 17-ketosteroids and formaldehydogenic steroids is to be contrasted with the decrease in 17-hydroxycorticoids.)

The desoxycorticosterone-like qualities of the steroid are further illustrated by the effects of corticosterone after bilateral complete adrenalectomy in a patient with hypertension. The administration of 50 to 100 mg. of free corticosterone by mouth,

and subsequently by injection, produced a recurrence of headache, weight gain, a significant elevation of blood pressure and an increase in cardiac size.

Cortisone-like effects. The administration of 50 to 100 mg. of corticosterone daily improves the response of patients with Addison's disease to hypoglycemia induced by insulin injection or prolonged fasting. It is of interest, however, that the rise in total nitrogen excretion obtained is minimal, even with doses as large as 300 mg. a day (Fig. 8).

Corticosterone has been shown to be capable of restoring to normal the characteristically slow electroencephalogram encountered in untreated or desoxycorticosterone-treated patients with Addison's disease. As might be expected from this finding, patients with Addison's disease may experience a

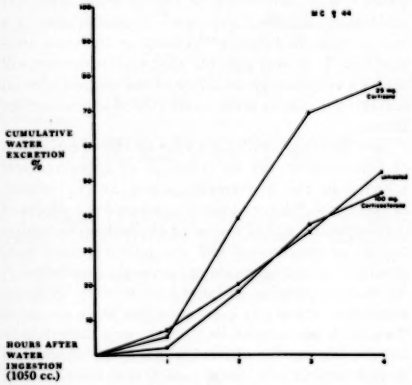


FIGURE 9. *Comparative Effects of Corticosterone and Cortisone on the Water Test in Addison's Disease.*
Water excretion expressed as per cent of water ingested.

definite increase in sense of well-being during corticosterone treatment. On the other hand, in doses up to 300 mg. a day, corticosterone has produced no significant change in the level of circulating eosinophils, and is considerably less effective than cortisone in restoring to normal the impaired capacity of the patient with Addison's disease to excrete an ingested water load (Fig. 9). No evidence of an effect on inflammatory or allergic processes has been reported.

Toxicity

No toxic effects of corticosterone have been described, other than those that may be considered to be an exaggeration of its physiologic action through overdosage. Because of the relatively potent salt-retaining effect of this compound in relation to its carbohydrate-regulating capacity, excessive salt and water retention may be observed in patients with Addison's disease with a dosage that is inadequate for satisfactory regulation of the electroencephalographic abnormality, the disturbance in water turnover and the tendency to fasting hypoglycemia.

Absorption and Fate

There is little knowledge concerning the mode of absorption of corticosterone. Physiologic activity after oral and intramuscular administration shows that absorption occurs by either route, but quantitative data are lacking.

Although 17-ketosteroids continue to be detectable in the urine of patients with Addison's disease maintained on corticosterone, this substance seems to be much less active as a precursor of 17-ketosteroids than either cortisone or hydrocortisone. This is illustrated by the striking differences in ketosteroid excretion of a patient with carcinoma of the prostate previously subjected to bilateral orchidectomy and total adrenalectomy. During a five-day period in which he was given 300 mg. of free corticosterone daily by mouth, 11.6 mg. a day was the highest level of ketosteroid excretion attained, and the mean output for the period was 9.8 mg. a day (Fig. 8). In contrast, with 300 mg. of oral hydrocortisone acetate (equivalent to 282 mg. of free hydrocortisone daily), urinary ketosteroids reached the impressive figure of 47.2 mg. a day; the values obtained during cortisone administration were intermediate. Similarly, measurement of the biologic androgenic activity of the urine in the same patient indicated that corticosterone was a much less effective precursor than either cortisone or hydrocortisone[77] although the absolute values for all three compounds were relatively low. Studies carried out by Wolfson et al.[78] have demonstrated still another difference in the urinary end-products derived from these hormones. A significant rise in urinary steroids detectable by the Pettenkofer colorimetric reaction (acid-furfural) was produced by the administration of corticosterone but not by cortisone or hydrocortisone. Since adrenal activation with ACTH also causes a rise in urinary Pettenkofer chromogens, these studies were considered to provide additional evidence for corticosterone as a primary secretory product of the adrenal cortex.

Excretion of formaldehydogenic ("11-oxy-") steroids in patients with adrenal insufficiency receiving maintenance doses of corticosterone appears to be the same as that seen in patients receiving cortisone. It is of interest to note, on the other hand, that the urinary excretion of total 17-hydroxycorticoids is not increased (Fig. 8). Since the latter procedure[79] measures chiefly corticosterone derivatives possessing a hydroxyl function on carbon-17, it is evident that

administered corticosterone does not undergo a significant degree of 17-hydroxylation. This is in agreement with the results of adrenal perfusion in vitro.[4]

Preparations and Dosage

At present limited amounts of free corticosterone are available for investigational use only in tablets for oral administration and in a saline suspension for intramuscular injection. In the maintenance of patients with adrenal insufficiency, the daily dose of corticosterone appears to be approximately 25 to 50 mg. by intramuscular injection or 50 to 100 mg. by mouth.

Clinical Uses

The clinical usefulness of corticosterone appears at present to lie principally in its potentialities as replacement treatment for patients with adrenocortical insufficiency. A few clinical trials have shown it to possess no antirheumatic activity.[80]

Limited experience in this clinic supports Conn's impression that corticosterone may prove satisfactory as the sole adrenal replacement in patients with Addison's disease. A thirty-three-year-old man with Addison's disease of two years' duration has been well maintained for four months on no treatment other than corticosterone, first intramuscularly and then by mouth. It was found that 50 mg. by injection was sufficient for maintenance of weight and electrolyte balance, but that 100 mg. was required by mouth to maintain the same beneficial effect. This is in accord with Conn's finding that intramuscular injection of corticosterone is two to three times as effective as the oral form. The patient's electroencephalogram is normal; his feeling of well-being equals that which he experienced on 25 mg. of cortisone daily. A mild crisis, precipitated by a respiratory infection, was satisfactorily controlled with no hormonal treatment other than 200 mg. of corticosterone intramuscularly.

A forty-four-year-old woman with Addison's disease has been treated with corticosterone alone for two months; she has not fared as well, however, as the patient just described. On 100 mg. of corticosterone daily by mouth she suffered from excessive salt retention, which required reduction of the dose to 50 and then to 35 mg. a day. At these levels of dosage she is free of edema but lacks a sense of well-being comparable to that produced by 25 mg. of cortisone acetate daily.

Thus, our preliminary impression is that corticosterone, which combines the therapeutic properties of desoxycorticosterone and cortisone in a preparation active by mouth, may be satisfactory as the sole maintenance treatment for some patients with Addison's disease. On the other hand, the same combination of properties may be a disadvantage in patients who prove to be more sensitive to the salt-retaining than to the carbohydrate-regulating properties of the hormone. Cortisone and desoxycorticosterone, given separately and therefore independently variable, appear to provide a more flexible method of controlling the requirements of patients with Addison's disease.

The relatively small increase in urinary output of 17-ketosteroids after oral administration of corticosterone is accomplished by only a moderate increase in metabolic products with androgenic activity. Corticosterone may therefore have a place in the specialized problem of the maintenance of the patient with carcinoma of the prostate who has undergone orchidectomy and adrenalectomy for the purpose of reducing the level of androgen production. It is also possible that corticosterone will act as a satisfactory inhibitor of the normal adrenal cortex in patients with cancer of the prostate or breast.

Few data are available so far on the effectiveness of corticosterone as an inhibitor of adrenocortical activity in the abnormally active adrenal gland. Wilkins et al.[81] have recently compared the effects of corticosterone and of cortisone on electrolyte regulation in a one-year-old girl with adrenogenital syndrome and accompanying adrenal insufficiency. Adrenal suppression as judged by urinary 17-ketosteroid excretion was more complete with cortisone than with corticosterone, which, however, had a definite effect. On the other hand, corticosterone in this patient was more potent than cortisone in causing sodium retention.

Compound A (11-Dehydrocorticosterone)

The history of Compound A (Fig. 10) is similar to that of corticosterone, described above. Dehydrocorticosterone was the first adrenocortical hormone with carbohydrate-regulating activity to be produced in quantities allowing adequate clinical investigation.[82] Early studies[83, 84] indicated that Compound A, like corticosterone, possessed both electrolyte-regulating and carbohydrate-regulating effects. Both actions were more easily demonstrated in patients with Addison's disease than in normal subjects.[85]

The intramuscular injection of 40 to 100 mg. of dehydrocorticosterone to patients with Addison's disease produced moderate salt and water retention, weight gain, a rise in blood pressure and an increase in cardiac size. Changes in intermediary metabo-

lism were less prominent, although small increases were observed in the excretion of urinary nitrogen, potassium, phosphorus and uric acid. The effects of the steroid on glucose and insulin tolerance were variable, but the occurrence of hypoglycemic symptoms during prolonged fasting was successfully prevented.

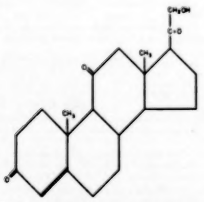


FIGURE 10. *Chemical Structure of 11-Dehydrocorticosterone (Compound A).*

The therapeutic uses of dehydrocorticosterone appear to be the same as those of corticosterone.

COMPOUND S

11-Desoxy-17-hydroxycorticosterone, or Compound S (Fig. 11), was first isolated in 1938 from beef adrenal glands by Reichstein and Von Euw. In 1940 the same workers accomplished its synthesis.[86]

In its physiologic action Compound S behaves like desoxycorticosterone.[54] Clinton and Thorn[87] observed a moderate decrease in urinary sodium and chloride in a dog given 25 mg. of Compound S by intramuscular injection. In 2 normal human subjects given 400 mg. of Compound S acetate daily by mouth for five days and 200 mg. of the hormone intramuscularly for five days respectively no changes in urinary sodium, potassium or chloride were noted.[88] Similar findings were obtained by Terry and London.[89] Pearson et al.[90] on the other hand, observed a slight retention of sodium chloride in 4 patients with chronic lymphatic leukemia who were given 200 mg. of Compound S acetate daily for ten to twenty-four days. We have obtained similar results in a patient who had undergone orchidectomy and bilateral adrenalectomy for metastatic carcinoma of the prostate and who was given 300 mg. of the hormone daily for four days by mouth. Compound S had no effect on calcium and phosphorus excretion.[90]

In doses up to 400 mg. a day, both by intramuscular and by oral administration in the human being, Compound S acetate appeared to have no influence on organic metabolism as measured by intravenous glucose tolerance tests and changes in serum total lipid and cholesterol and urine glucose, uric acid, creatinine and total nitrogen.[88, 90]

Compound S exhibited a weak ACTH-suppressing activity in the rat.[54] The hormone showed no effect on the response of adrenalectomized rats to water loading.[54] No eosinophil response followed either the oral or the intramuscular administration of Compound S acetate to man.[88, 89] In contrast to cortisone and hydrocortisone, this hormone was without effect on the lymphatic tissue of patients with chronic lymphatic leukemia.[90]

That Compound S may be absorbed from the gastrointestinal tract is indicated by the rise in urinary 17-ketosteroids that occurs when the hormone is given by the oral route.[88] Fajans et al.,[85] however, found no increase in urinary 17-ketosteroids when the hormone was administered by intramuscular injection to a normal man in a dose of 200 mg. daily for five days. In neither case was there any appreciable rise in urinary formaldehydogenic steroids. Polley and Mason,[91] however, found slight increases in the urine of both 17-ketosteroids and formaldehydogenic steroids after the intramuscular administration of 200 mg. of Compound S acetate daily for seven days to a patient with rheumatoid arthritis. We have observed a considerable rise in the urinary excretion of 17-hydroxycorticoids in a patient who had undergone orchidectomy and bilateral adrenalectomy for metastatic carcinoma of the prostate and who received 300 mg. of Compound S acetate by mouth daily for four days. Hechter et al.[4] reported that the perfusion of Compound S through beef adrenal glands caused the formation of 17-hydroxycorticosterone (Compound F).

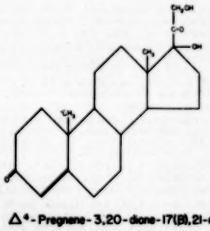


FIGURE 11. *Chemical Structure of 11-Desoxy-17-Hydrocorticosterone (Compound S).*

Compound S acetate has been found to be without effect in rheumatoid arthritis[91] and chronic lymphatic leukemia.[90] No cases of its use in other diseases have been reported.

(To be continued)

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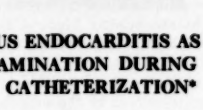
MEDICAL INTELLIGENCE



INFECTIOUS ENDOCARDITIS AS A RESULT OF CONTAMINATION DURING CARDIAC CATHETERIZATION*

PAUL WINCHELL, M.D.†

MINNEAPOLIS

A SEARCH of the medical literature through 1950 does not reveal any reported cases of bacterial endocarditis following cardiac catheterization. The following case seems to represent an example of temporal and probably causal relation.

CASE REPORT

A 44-year-old woman was first admitted to the hospital on November 28, 1951. There was a well substantiated history of rheumatic fever at the age of 10, but there were no symptoms of any kind until 1943, when she noted the onset of dyspnea. A diagnosis of mitral stenosis was made, and digitalis therapy was started in 1946. In November, 1950, she apparently experienced an episode of rapid auricular fibrillation. At about the same time there was a cerebral embolus and transient right hemiplegia lasting only a few minutes. Subsequently, she continued to have auricular fibrillation and was able to undertake only limited activity even though the ventricular rate was well controlled with digitoxin. She entered the hospital for evaluation regarding mitral commissurotomy. Studies confirmed the diagnosis of mitral stenosis with chronic auricular fibrillation, and an appointment for cardiac catheterization was made.

The patient was readmitted to the hospital on January 15, 1952, when the findings were the same as those on the original admission. On January 17, she was subjected to cardiac catheterization, having received 300,000 units of procaine penicillin on the previous evening and twice on the day of cardiac catheterization. The studies at that time confirmed the presence of a moderate degree of pulmonary hypertension. On January 19, 100,000 units of crystalline penicillin intramuscularly every 6 hours was begun, and on January 22 she was taken to the operating room for mitral commissurotomy. She had been quite anxious before going to the operating room and on induction of anesthesia, the pulse increased to approximately 140 beats per minute, the rhythm continuing to be that of auricular fibrillation. She was observed for approximately 1 hour, after which operation for that day was canceled. She continued to receive penicillin, however.

On January 28, 11 days after cardiac catheterization, the patient was found to have a temperature of 101.2°F. and tachycardia. System review at that time disclosed no positive findings. Physical examination revealed auricular fibrillation at a rate of 132 per minute. There was very slight right-costovertebral-angle tenderness. There was a tiny area of erythema at the tip of the left middle finger. Cultures of the blood and urine were taken, and supplementary digitoxin was given. On the following day, the white-cell count was 11,200, with 83 per cent neutrophils. There was a marked left shift of the neutrophils. The blood culture that had been taken on the 1st day of illness contained an alpha-hemolytic streptococcus, which was grown from the broth flask and not from the pour plates. All remaining cultures of both blood and urine were sterile. The temperature continued to rise each day, reaching a maximum of 105°F. by rectum on January 30.

A diagnosis of infectious endocarditis was made on the basis of the clinical picture in addition to the positive blood culture, and 500,000 units of penicillin intramuscularly every 4 hours, as well as 1,000,000 units of penicillin intravenously 3 times a day, was begun. In addition, she received 0.5 gm. of streptomycin twice daily intramuscularly. There

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was a prompt response to this treatment, the patient becoming afebrile by February 1 and remaining so throughout the entire period. Streptomycin was discontinued on February 13, but the penicillin was continued for a full 6 weeks' course. She has remained clinically well, although still under observation for a possible recurrence of the endocarditis. All blood cultures taken after discontinuance of the treatment have been sterile. The sedimentation rate, which reached a maximum value of 38 mm. per hour, is now 21 mm. per hour.

Sensitivity studies on the alpha-hemolytic streptococcus were done and are as follows: the organism was sensitive to 3.9 units of penicillin and resistant to 62.5 microgm. of streptomycin per cubic centimeter, and sensitive to 31.2 microgm. of aureomycin, 62.5 microgm. of chloramphenicol and 62.5 microgm. of terramycin per cubic centimeter.

Discussion

All the instruments and the catheter had been prepared by standard washing and autoclaving technics. The procedure was carried out with aseptic precautions.

When it became apparent that the febrile illness might be related to the cardiac catheterization, a careful bacteriological study of the materials and equipment was made. Attention was immediately called to the recording apparatus, a Hamilton manometer joined to the catheter by lead tubing. A leveling bottle containing sterile water and sterile mineral oil was a necessary unit in the system, and it was soon found that the fluid filling the manometer contained large numbers of gram-positive and gram-negative rod and coccal forms. Swabs of the interior of the manometer contained similar organisms. None of the remaining fluids used intravenously or other equipment yielded growth on culture. It seemed likely, therefore, that during cardiac catheterization a variety of organisms had been introduced directly into the blood stream.

An unusual feature of this case was the development of the infection while the patient was receiving fairly large amounts of penicillin before operation. The sensitivity studies are helpful in this respect in that the organism isolated from the blood culture was penicillin resistant.

It can be argued that the time lapse between supposed inoculation and the development of symptoms is too short to support a causal relation and that endocarditis coincidentally developed after cardiac catherization. The weight of evidence, however, does not tend to support such a point of view.

Summary

A case of infectious endocarditis as a result of contamination during cardiac catheterization is reported.

Infectious endocarditis should probably be considered as a possible complication when one is evaluating the risks of the procedure.

DOCTORS AFIELD

Friedrich Schiller

Robert W. Buck, M.D.

BOSTON

HALF a century or more ago, but well within the adult memory of several million persons now living in this country, road companies from Cincinnati or Chicago were presenting *Wilhelm Tell* in the original German throughout the Middle West to good-sized audiences of emigrés from the Palatinate. The German influence represented the major foreign component in the American scene of the latter nineteenth century. As late as 1916 Harvard Medical School gave office room to "privatdocents," and laboratory handymen were still universally called "Dieners." To that generation the name of Friedrich Schiller, Swabian dramatist, historian and poet of the pigtail era (German, *Zopfzeit*), and for a few months of his forty-five years a practicing physician, was not unfamiliar. Probably today no one but an occasional student of modern languages reads *Wilhelm Tell* or *Don Carlos* or the *History of the Thirty Years' War*.

Schiller was not a doctor afield; he was a refugee from medicine. Born in 1759, he received his medical certificate in November, 1780, at the age of twenty-one. James Parkinson and Caleb Hillier Parry were also just starting out. Benjamin Rush, aged thirty-five, was writing in Philadelphia of dengue fever. William Withering, aged thirty-nine, was trying out the effect of foxglove in dropsy, and Benjamin Franklin had just invented bifocal glasses. Neither the Massachusetts Medical Society (1781) nor the Harvard Medical College (1782) had yet been born.

The German historian of the Thirty Years' War was a horrified observer of the neighboring French Revolution. He predicted that it would give rise to a state of anarchy out of which "a capable strong man will appear from some quarter and make himself master not only of France but also, perhaps, of a large part of Europe" — an interesting instance of poetic clairvoyance. Oddly enough, along with a number of other foreigners who had "defended the cause of the people against the despotism of kings," such as George Washington, Pestalozzi, Kosciusko and Anacharsis Cloots, he was granted honorary citizenship in the new French Republic. The diploma was phonetically inscribed to "*M. Gillé, publiciste allemand.*"[1]

Schiller's father was a barber surgeon who became a captain in the pitiable army of the Duke of Württemberg, and later took up landscape gardening. The boy Friedrich was selected by young Duke Karl Eugen with a few other officers' sons to attend his newly established academy, which eventually developed into a university with a school of medi-

cine. Schiller did well enough in his studies, although his maturing talents were entirely literary, and after failing to obtain his medical diploma with a thesis on the philosophy of physiology, he wrote his first drama *The Robbers*. In the following year (1780) he was successful with a dissertation entitled "The Relation between Man's Animal and Spiritual Nature," and became an army surgeon (without rank). His job was to care for a hospital ward and appear daily on parade. His salary was 18 florins a month, about a tenth of what an average physician

FIGURE 1. *Schiller's Graduating-Class Picture, Karlsschule Medical School, 1787 (Reproduced from Magnus[4]).*

in private practice might expect to earn in a sizable German city of the time.[2]

The Robbers was such a success that the author was ordered by the Duke to confine himself strictly to his medical duties or be cashiered. Schiller chose to flee to Mannheim in the Palatinate, a deserter with a price on his head. Although two years later he still protested in a letter to his friend and producer Dalberg that a medical career was nearest to his heart, he never again laid his hand to a scalpel or prescribed a pill.

German if not European medicine of Schiller's day was dominated by the influence of Boerhaave, of Albrecht von Haller (author of more than 13,000 scientific papers) and John Peter Frank, whose notable work on public health was issued by the same printer who published *The Robbers*. Schiller's medicine was theirs.

Four of his medical papers survive: his first unsuccessful thesis, in fragmentary form only; the successful dissertation on man's animal and spiritual nature (a tedious essay that may be consulted in any collected edition of his works); a series of clinical notes on a neurasthenic fellow student in Duke Karl's academy; and a Latin dissertation *De discrimine febrium inflammatorium et putridarum*.

The ancient distinction between inflammatory and putrid (in England, Cullen preferred the classification synochus and typhus) or paroxysmal and continued fevers was partly clinical, but mainly theoretical, depending in part upon whether it was conceived that the cause lay in a disturbance of the blood and its circulation, or in the humors and the nerves. Schiller, following Boerhaave, attributes inflammatory fevers to obesity or plethora, putrid fevers to *ataxia nervorum* leading to mischievous vitiation of the bile.[3]

It might be interesting to try to reconcile the clinical observations of the systematists with their theoretical interpretations in the light of contemporary medical philosophy, but Schiller's essays are not the product of original observation or thought, and hence not a proper source of information.

Little has been found in the bulk of his literary works to betray his youthful medical training — not nearly so much as Shakespeare exhibited without benefit of a medical degree. And, more unfortunately, his medical education was quite powerless to help him prolong his life or avoid any of the distressing symptoms of the pulmonary disease that carried him off before his great contemporary Goethe had published the first part of *Faust*.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39061

PRESENTATION OF CASE

First admission. A seventy-four-year-old man was referred to the hospital because of weakness and pain in the back.

The patient was apparently well until about three years before entry, when he fell from a small step-ladder and sustained a comminuted fracture of the surgical neck of the right humerus. He was admitted to another hospital, and on the following morning urinary retention developed. Catheterization revealed gross hematuria. He was placed on constant drainage and progressed satisfactorily without recurrence of hematuria; later, however, when the catheter was removed, he was unable to void. The catheter was replaced, and he was transferred to still another hospital, where a suprapubic prostatectomy was done. The prostate was reported by the pathologist as showing adenocarcinoma, Grade 2, without invasion of the prostatic capsule. After operation the patient was placed on Estinyl; this therapy was continued until three months before admission, when medication was changed to stilbestrol, 15 mg. daily. This was followed by generalized pruritus and a severe rash on both legs, and the dose was therefore reduced to 5 mg. daily. He was later treated with Tace (a compound having an estrogenic activity), one capsule three times daily until three weeks before admission, when all estrogen therapy was stopped. During the last three months he complained of generalized weakness, loss of appetite, dry mouth, and some hoarseness. Roentgenograms of the chest, pelvis and lumbar spine were normal except for moderate hypertrophic arthritis of the lumbar spine. He was placed on antianemic therapy, but he gradually became much weaker and about one month before entry was admitted to still another hospital, where the blood was normal on routine examination; examination of the urine was negative except for a specific gravity persistently ranging from 1.002 to 1.005. He was given one transfusion and was discharged on the ninth hospital day. He continued to complain of hoarseness, excessive thirst and urination, nocturia (six times), lumbar backache, generalized weakness, loss of appetite and moderate constipation. He was given daily injections of Pitressin tannate in oil (5 pressor units) during the two weeks before entry, with questionable improvement in the polyuria and polydipsia. He continued to complain of weakness and pain in the back, and was referred to this hospital.

On physical examination the patient was thin and gaunt but was in no acute distress. The voice was hoarse. There was no cyanosis or icterus. An area of dark-brown pigmentation was present on the right side of the scalp. The right pupil was larger than the left, but both reacted to light and accommodation. The neck was normal. There were fine inspiratory rales over the right base and diminished breath sounds over the middle lobe. The apex of the heart was 11 cm. to the left of the midsternal line. The aortic second sound was greater than the pulmonic. There was a mass in the left axilla, said to have been present since the age of ten, and a tender, ill defined, irregular mass in the right upper quadrant was felt only by the admitting resident. There was bilateral costovertebral-angle tenderness, greater on the right than on the left. The prostatic bed was irregular but without definitely palpable masses. The extremities were normal.

The temperature was 97°F., the pulse 100, and the respirations 18. The blood pressure was 180 systolic, 90 diastolic.

The urine was light amber, had a specific gravity of 1.012 and was normal except for the sediment, which contained 8 white cells per high-power field and calcium phosphate crystals. Examination of the blood revealed a hemoglobin of 12.8 gm. and a white-cell count of 17,400, with 79 per cent neutrophils, 14 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophils. The smear was negative for myeloma cells. The blood sugar was 106 mg., the acid phosphatase 0.6 units, the alkaline phosphatase 4.8 units, the total protein 6.45 gm., the albumin 5.45 gm., the globulin 1.00 gm., the nonprotein nitrogen 58 mg., the calcium 12.7 mg. and the phosphorus 3.4 mg. per 100 cc.; the sodium was 135.2 milliequiv., the chloride 95 milliequiv., and the potassium 4.4 milliequiv. per liter. The blood Wassermann test was negative. The sedimentation rate was 57 mm. in one hour. A twenty-four-hour urine calcium determination was 14.8 mg. per 100 cc. or 310 mg. per twenty-four hours. A phenolsulfonephthalein test showed 50 per cent excretion in two hours. In three overnight urinary specimens the highest specific gravity was 1.014. A urine specimen was negative for Bence-Jones protein; the urinary chloride was 34 milliequiv. per liter. A basal metabolic rate was + 12 per cent (satisfactory test); the uptake of radioactive iodine was 11.4 per cent in forty-eight hours (normal, 25 to 50 per

cent). A prostigmine test was negative for myasthenia gravis. The blood Widal reaction and agglutination for brucella organisms were negative. A urine culture grew out a moderate number of diphtheroids and a few colonies of *Staphylococcus albus*; a blood culture was negative in two flasks. A roentgenogram of the chest showed scarring in the right upper lobe, with some reduction in size, a rounded density in the right second anterior interspace, a few scars in the left apex and a normal heart shadow. A barium-swallow examination demonstrated minimal but constant deviation of the esophagus to the right just above the clavicle at the projected level of the first and second thoracic vertebras. The trachea was not displaced. There was moderate degenerative change in the cervical space between the fifth and sixth cervical vertebras, with narrowing of the fifth interspace. A lateral film of the skull demonstrated no bony abnormality. Spot films of the fourth lumbar vertebra revealed degenerative changes but no evidence of bone destruction. The transverse processes were rather small and were not as well ossified as those above and below. On intravenous pyelogram the kidneys were within normal limits of size and shape. Excretion was slow and in poor concentration, so that visualization of the calyxes and pelves was inadequate for diagnosis. No calculi were identified in the course of the urinary tract. The bladder was normal.

In the hospital the patient became progressively weaker. A laryngoscopist found the vocal cords normal in color. Movements were good, but the cords did not approximate in the middle because of a "bowing" effect. The left vocal cord was thinner than the right; there was no ulceration or tumor. The sedimentation rate and white-cell count remained elevated, and on the fourteenth hospital day a picket-fence type of fever, with temperature elevations to 101°F., developed. The pulse ranged from 90 to 120; respirations were normal. An iliac-crest bone-marrow aspiration was read as normal. Repeated calcium and phosphorus determinations confirmed the previous findings. The patient was discharged on the twenty-fourth hospital day with a note saying "4 balls and no strikes." While in the hospital he had gained 3 pounds in weight and felt stronger.

Final admission (seven weeks later). The first few weeks at home the patient felt much better and went out to drive and then suddenly two weeks before admission he rapidly began to fail. His appetite was poor, and he lost 5 pounds in weight. Generalized weakness was progressive, and during the week before admission he was unable to get out of bed without support. He felt drowsy much of the time and "ached all over." Hoarseness and nocturia had persisted.

On physical examination the patient appeared chronically ill and debilitated, and tended to fall asleep between questions. At times he was confused. The lungs were clear except for a bronchial quality to the breath sounds in the upper lung fields posteriorly. There was a Grade 1 aortic and apical systolic murmur. The abdomen was soft and nontender. The liver and spleen were not palpably enlarged; there were no masses. Otherwise the general examination was negative.

The temperature was 100°F., the pulse 120 and the respirations 28.

The urine had a specific gravity of 1.012 and gave a +++ test for albumin; the sediment contained 2 red cells, 40 white cells with a few clumps and many coarsely granular and finely granular casts per high-power field. Examination of the blood revealed a hemoglobin of 7.4 gm. and a white-cell

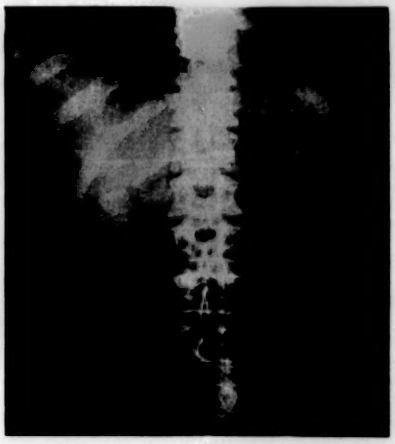

FIGURE 1. *Roentgenogram of the Pelvis.*
The arrow points to the mass lying above the right kidney.

count of 29,700, with 83 per cent neutrophils, 11 per cent lymphocytes and 6 per cent monocytes. The total protein was 6.25 gm., the albumin 4.12 gm., the globulin 2.13 gm., the nonprotein nitrogen 85 mg., the acid phosphatase 2.3 units, the alkaline phosphatase 11.6 units, the calcium 15.6 mg., and the phosphorus 5.0 mg. per 100 cc.; the sodium was 135.0 milliequiv., the chloride 98 milliequiv., the potassium 4.4 milliequiv., and the carbon dioxide 28.2 milliequiv. per liter. A repeated chest film was reported as showing no intrinsic disease. A second barium-swallow examination showed the same findings as before. Roentgenograms of the spine and pelvis did not reveal any localized bone destruction or cystic changes. An ill defined density was

present above and superimposed in part on, the upper pole of the right kidney (Fig. 1). The lower pole of the right kidney lay more medially than usual. A review of the previous films disclosed the mass previously present; it had not changed appreciably in the intervening period.

On the fourth hospital day the patient suddenly became worse. He seemed to be strangling on thick, blood-tinged mucus. The blood pressure was 90 systolic, 30 diastolic. The pulse was 88 but varied markedly in intensity. Respirations were of a Cheyne-Stokes type, with periods of apnea up to 30 seconds. An electrocardiogram was not diagnostic and was considered to be probably within normal limits. Moderate jaundice appeared during the second week in the hospital. He was given transfusions, with only temporary improvement. During most of this admission he had a persistently elevated temperature of 100 to 102°F., and the pulse ranged from 60 to 130. Treatment included 300,000 units of penicillin daily. He became less responsive; the nonprotein nitrogen rose to 78 mg. per 100 cc., and he died on the thirteenth hospital day.

Differential Diagnosis

Dr. Walter Bauer*: "A prostigmine test was negative for myasthenia gravis." I do not know just why this was done. The patient did have hoarseness, but there was nothing else in the history suggestive of myasthenia gravis.

May I see the x-ray films? Are you going to be helpful this morning, Dr. Hanelin?

Dr. Joseph Hanelin: I think I shall be very helpful. The first chest examination shows the changes described in the protocol in the right upper lung and also at the left apex. There is evidence of scarring at the apexes, and a small, well defined nodule about 1 cm. in diameter is projected within the right second interspace. The examination of the chest during the last admission was not made in the same manner; the patient was too ill to stand, and the film is an anteroposterior instead of the usual posteroanterior projection; therefore, it is possible that the same changes were present but are not shown.

Dr. Bauer: So you cannot say whether the lesions have disappeared or are not demonstrable.

Would you say the ribs are absolutely normal?

Dr. Hanelin: I see no focal areas of destruction in the ribs. In the spine there are generalized degenerative arthritic changes. There is a suggestion of possible destruction along the right lateral aspect of the body of the fourth lumbar vertebra. There is some loss in height of the fifth lumbar body. Again, I cannot say if that is due to any definite intrinsic lesion. The important finding in the abdominal films is that of a mass, which lies above the right kidney and is partially superimposed upon it (Fig. 1). The right kidney lies lower in position than usual, and the lower pole has swung medially.

Dr. Bauer: Could the mass be the adrenal gland?

Dr. Hanelin: Yes.

Dr. Bauer: You do not see anything comparable to it on the other side.

Dr. Hanelin: No. In this film of the barium-swallow examination the displacement of the esophagus, which deviates to the right in the lower portion of the neck, is the type not infrequently seen with tumors of the parathyroid.[1]

Dr. Bauer: Is there any reason why an enlarged lymph node could not do the same thing?

Dr. Hanelin: No reason except that is a rather unusual site for a metastasis in a lymph node.

Dr. Bauer: Will you show me the films of the skull?

Dr. Hanelin: I see nothing abnormal in them.

Dr. Bauer: Thank you, Dr. Hanelin. I hope your interpretations will prove helpful to someone in the audience.

I can truthfully say I do not know the nature of the disease that this patient had. I can say a few words about the character of his death and the interpretation of his symptom complex. From there on, I shall be guessing. From the evidence at hand, it seems safe to conclude that this seventy-four-year-old man suffered from demineralization of the bones, hypercalcemia, hypercalciuria, renal insufficiency and death. However, I am at a loss to explain the nature of the bone disease that led to this sequence of events. Whether his renal disease was due to renal calcinosis, renal stones or calcium gravel with associated pyelonephritis, I cannot say. I do think that all the symptoms (polydipsia, polyuria, nocturia, backache, generalized weakness, loss of appetite and moderate constipation) except the hoarseness can be accounted for on the basis of hypercalcemia. My problem, then, is to try to determine the cause of the hypercalcemia.

The patient did receive estrogen therapy, first Estinyl and later stilbestrol. Such therapy can on occasions cause hypercalcemia, which, if it is sufficiently severe and not recognized, can cause death. In this case estrogen therapy was discontinued approximately three months before admission. With the knowledge that the hypercalcemia of estrogen therapy disappears promptly (within a few days to a few weeks) after discontinuance of estrogen therapy, it seems safe to conclude that the hypercalcemia was not due to the hormones administered.

The minimal but constant deviation of the esophagus to the right could have been caused by a parathyroid tumor or by an enlarged lymph node. Whatever my diagnosis, I must attempt to explain the esophageal deviation, the one small lesion in the lung and the mass above the right kidney. The last I shall assume to be an adrenal gland. I must also account for the hepatic impairment observed during the last few weeks of this patient's illness.

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Rather than run the gamut of diagnostic possibilities, I shall limit my considerations to three diseases: carcinoma of the prostate, with widespread bone metastasis, hyperparathyroidism and multiple myeloma.

Carcinoma of the prostate with associated widespread bone metastasis can cause hypercalcemia, hypercalciuria and an increase in the alkaline phosphatase. However, I do not think the findings in this case were due to metastatic prostatic carcinoma. The chemical findings as recorded indicate active demineralization. This degree of demineralization, when due to metastatic carcinoma from the prostate, should be accompanied by x-ray changes and a much higher alkaline phosphatase. It is for this reason that I discard the diagnosis of metastatic cancer.

I am sure that one must consider hyperparathyroidism, although I doubt the correctness of this diagnosis, even though the serum calcium was elevated. However, the serum phosphorus was normal. One might argue that the degree of renal impairment present was sufficient reason for the failure of the serum phosphate to fall. The alkaline phosphatase was elevated, 11 units per 100 cc. From my experience with hyperparathyroidism, I would expect a much higher alkaline phosphatase if the hyperparathyroidism was sufficiently marked to cause a serum calcium of 15.6 mg. per 100 cc., and a twenty-four-hour urinary calcium excretion of 310 mg. These findings indicate active demineralization, which, if it is due to hyperparathyroidism, suggests the presence of severe disease. By all the rules of the game, the alkaline phosphatase should have been higher if this patient was suffering from hyperparathyroidism. Therefore, I shall discard that diagnosis.

The third diagnostic consideration that I mentioned was multiple myeloma. I believe that this disease could account for all the findings recorded in the case history. To be sure, it is hazardous to make a diagnosis of multiple myeloma in the absence of plasma cells and Bence-Jones protein in the urine. My reason for seriously entertaining this diagnosis is the finding of a serum globulin of 1 gm. per 100 cc. At the moment, I can think of no cause for this abnormality other than multiple myeloma. I trust it was not a laboratory error. In such a case included in Snapper's[2] book on bone diseases the total protein was 6.57 gm., the serum globulin 4.76 gm., and the serum albumin 1.25 gm. per 100 cc. In cases of this type, most of the Bence-Jones protein is precipitated out with the serum albumin by the procedures routinely employed for determining the albumin-globulin ratio.

In making the diagnosis of multiple myeloma, I am forced to conclude that the patient had some extraosseous lesions. Though they are not a common finding in multiple myeloma, they do occur. Could such extraosseous lesions account for the deviation of the esophagus, the pulmonary lesion and the enlarged right adrenal gland? These findings and the terminal jaundice could have been part and parcel of the same pathologic process. I would be the first to admit that I have no way of proving my point. Rather than continue the discussion longer, I shall say that this man had multiple myeloma with extraosseous involvement. I am assuming that the multiple myeloma was responsible for the previously mentioned demineralization, hypercalcemia, hypercalciuria, renal disease, renal failure and death. He may have had renal calculi or calcium gravel and a mild pyelonephritis. He also suffered from hypertensive heart disease. In a patient with multiple myeloma, there is always the possibility of amyloid deposition in various structures and organs. It is possible that some of the lesions that I have interpreted as extraosseous manifestations of multiple myeloma represented amyloid deposits.

I am sure that many of you in the audience have quite different opinions about the nature of this man's disease. I shall be glad to try to answer questions concerning any findings that you think I have left unexplained. I trust that other diagnoses will be suggested.

Dr. Joseph C. Aub: I want to know why you did not pay more attention to the mass in the kidney.

Dr. Bauer: I assumed that it was the adrenal gland and not the kidney.

Dr. Aub: How about a hypernephroma?

Dr. Bauer: I think the lesion is well defined and superimposed upon the kidney and not part of it.

Dr. Bernard M. Jacobson: Are you not worried about making a diagnosis of myeloma without a positive bone-marrow biopsy and with an elevated alkaline phosphatase?

Dr. Bauer: No; there are a few cases in the literature in which serum alkaline phosphatase levels of 10 to 12 units per 100 cc. have been observed. What I dislike most about making a diagnosis of multiple myeloma in this case must be very evident to all of you I am hanging my hat on one small peg — namely, a reported serum globulin of 1 gm. per 100 cc. However, as I said before, multiple myeloma is the only disease I can think of at the moment that will account for this abnormality.

A Physician: Can you make a diagnosis of multiple myeloma without an abnormal globulin?

Dr. Bauer: There are such cases on record. As stated before, the abnormal globulin (Bence-Jones protein) is precipitated out with the serum albumin. Therefore, one fails to demonstrate the abnormal globulin. The easiest way to demonstrate the presence of Bence-Jones protein in a case of this type is study of the serum by means of electrophoresis.

Dr. Jacobson: What about the bone marrow?

Dr. Bauer: We have on occasions failed to demonstrate plasma cells in bone-marrow aspirations.

DR. ALEXANDER LEAF: I wonder if all the values of the chemical determinations of serum calcium and phosphorus at the end of the first admission could be read. As I recall, they were quite interesting — particularly the serum phosphorus.

DR. BENJAMIN CASTLEMAN: The calcium was 12.7, 11.5 and 14.1 mg. on 3 separate samples, and the serum phosphorus 3.4, 3.4 and 2.6 mg. per 100 cc. respectively.

DR. BAUER: What did you have in mind?

DR. LEAF: I thought that the drop in serum phosphorus to 2.6 mg. with an elevation of the serum calcium to 14.1 mg. per 100 cc. at a time when we thought his renal function had improved slightly could not be disregarded.

DR. AUB: Multiple metastases of a carcinoma of the prostate do not have to be accompanied by high acid phosphatase. The acid phosphatase can be normal, even when the metastases are in bone. The metastases are usually large and obvious; those of hypernephroma may be tiny and widespread.

DR. BAUER: This degree of demineralization due to metastatic carcinoma of the prostate should have been accompanied by x-ray changes of the bones and a higher alkaline phosphatase, with or without elevation of the acid phosphatase — though I would expect the latter to have been elevated.

DR. AUB: It can happen.

DR. WARREN POINT: Dr. Bauer, how can you so readily dispose of the diagnosis of hyperparathyroidism?

DR. BAUER: I do not think there was much to say for that diagnosis. I believe the findings that suggest such a diagnosis represent a Clinicopathological Conference red herring. Although the serum calcium was elevated the serum phosphorus was normal. The latter finding could, of course, be accounted for by the renal failure. Even if this is the true explanation for the normal serum phosphorus, I would expect hyperparathyroidism sufficiently severe to cause a serum calcium value of 15.6 mg. per 100 cc. to be accompanied by a much higher serum alkaline phosphatase. We do not have many cases of hyperparathyroidism on record in which the daily urinary calcium excretion was 310 mg.

DR. FULLER ALBRIGHT: I should like to ask Dr. Aub whether he has seen hypercalcemia produced by estrogen therapy except in the presence of metastatic cancer of the breast.

DR. AUB: I do not know, because we do not give such large doses except in this condition.

DR. BAUER: I have been told of a patient with naturally occurring hyperesterinism who had a marked hypercalcemia; is that right?

DR. ANNE FORBES: That patient had an ovarian carcinoma.

DR. CASTLEMAN: The patient under discussion was shown last summer at Medical Grand Rounds, as a patient of Dr. Earle Chapman. Everybody chided Dr. Chapman after he presented the case and asked why he did not have this patient operated on for parathyroid adenoma. He thought at that time that the hypercalcemia had something to do with the estrogen therapy, I believe.

Before the autopsy, when this abdominal mass was felt more definitely, although it had been felt by Dr. Farahe Maloof on the first admission, it was believed that the diagnosis was hypernephroma. The patient was too sick to have any further studies done. We have had 2 cases in the past of hypernephromas with and without metastases, 1 with a large solitary metastasis and the other with no metastases, in which there was a hypercalcemia and a normal phosphorus. So that it was believed that Dr. Chapman was wise in not having the patient explored in spite of the change in the esophagus.

CLINICAL DIAGNOSES

(Hypercalcemia.)
?Hypernephroma, right kidney, with metastases.
(Uremia.)

DR. WALTER BAUER'S DIAGNOSES

Multiple myeloma, with extraosseous lesions.
?Renal calculi.
?Pyelonephritis.
?Secondary amyloidosis.
Hypertensive heart disease.

ANATOMICAL DIAGNOSES

Hemangiosarcoma of liver, with metastases to right adrenal gland.
(Hypercalcemia.)
Carcinoma of prostate.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy we were immediately interested in the abdominal mass. In this picture one can see the liver, the gall bladder pushed slightly to one side, and the kidney over which is this large mass well seen on the x-ray films (Fig. 2). The mass proved to be the adrenal gland, tremendous in size and completely replaced by yellowish necrotic tumor. It was directly contiguous with a large yellowish, necrotic mass, which involved almost half the right lobe of the liver. The liver tissue surrounding the mass was quite soft and somewhat necrotic. Seeing this in the gross we believed that it was a primary cancer of the adrenal gland, with metastases to the liver. We looked for stigmas of Cushing's syndrome but could find none.

With the radiologist present, I personally examined the neck very carefully and found nothing to suggest a parathyroid tumor. I spent an hour looking for the parathyroids within the neck and mediastinum and found 3 in the neck that looked perfectly normal microscopically. It is still conceivable that we missed the fourth parathyroid with a tumor in it. I am convinced, and so is the radiol-

ogist who was present, that there was not a parathyroid adenoma in the region of the esophageal defect seen on the x-ray film. All we could find was fat tissue. The bones looked perfectly normal on the gross examination. The small nodule in the lung seemed to be tumor; we thought it was a metastasis from the adrenocortical carcinoma. The prostate was tremendous in size and was extensively

FIGURE 2. *Autopsy Specimen, Showing the Tumor of the Liver* (A) *and the Tumor of the Adrenal Gland* (B).

involved with carcinoma; in fact the carcinoma had invaded one of the seminal vesicles. We toyed with the idea that the lesions in the adrenal gland and liver were metastases from the cancer of the prostate, although we found no enlarged lymph nodes in the abdomen, to which a prostatic carcinoma usually metastasizes first. Moreover, when such a carcinoma metastasizes to the bones, it is usually to the pelvic bones, which appeared normal in the x-ray films. The spine looked normal grossly.

The microscopical sections were quite a surprise. A section of the mass in the liver showed a tumor composed of varying degrees of vascular stalks and sinusoids lined with tumor cells; it seemed almost like the ordinary hemangioma that is commonly found in the liver except that the cells that lined the vascular spaces were malignant cells (Fig. 3). In the less differentiated areas, these channels were lined with tumor cells with numerous mitoses. It was a wild hemangiosarcoma, which did not look at all like the tumor that was found in the prostate. The tumor in the prostate was the usual type of slowly growing small-cell adenocarcinoma, with a great deal of fibrous tissue surrounding nerves (Fig. 4) and extension to the seminal vesicles. The kidney revealed very severe calcinosis; the calcium was deposited in the tubules as well as in the interstitial tissue. The most startling finding was within the lung, almost every alveolus and artery being lined with calcium — the most extreme calcification that I have ever seen in a lung. Examination of the bones demonstrated very little.

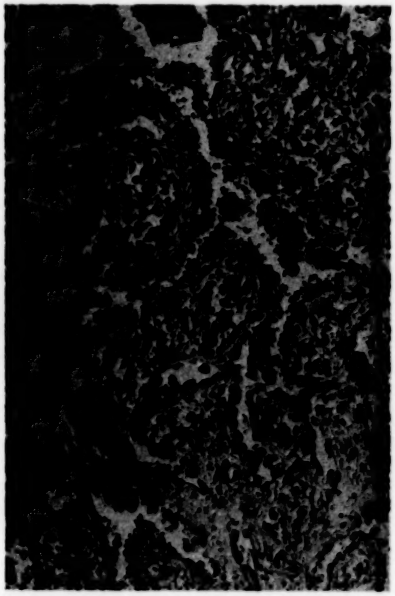

FIGURE 3.

DR. BAUER: Where were the blocks taken from?

DR. CASTLEMAN: The vertebras. There was one block that did give evidence of bone resorption of the trabeculae — a patch of fibrous tissue and a few osteoclasts. If we had seen that in a number of areas we should have considered early osteitis fibrosa. I suppose that can occur with the hypercalcemia from whatever cause. I do not believe we can completely rule out hyperparathyroidism because we did not find the fourth parathyroid

and might have missed it; on the other hand — and I should like to get the opinion of Dr. Albright about this — in the cases we have seen with calcinosis due to hyperparathyroidism, the parathyroid adenoma has been good sized, and there has been evidence of severe bone disease.

DR. ALBRIGHT: They have certainly been of good size, and, as far as I remember, bone disease has been present.

DR. CASTLEMAN: Perhaps the primary tumor in the liver may have produced parathyroid hormone. Hasn't Collip found that assays of tumors other than primary parathyroid tumors have some parathyroid hormone?

FIGURE 4.

DR. ALBRIGHT: I think Dr. Castleman is referring to a patient who came to autopsy in 1950.[3] From the blood chemical constituents before death it was quite clear that he did have hyperparathyroidism. At post-mortem examination there was cancer tissue everywhere, and it was not certain where the primary source was. Dr. J. B. Collip, of the University of Western Ontario, kindly assayed the tumor tissue for parathyroid hormone and found that the extract from the cancer tissue contained about the same amount of parathyroid hormone as a similar extract of beef parathyroid tissue.

DR. CASTLEMAN: I was under the impression that some other carcinomas might produce parathyroid hormone.

DR. ALBRIGHT: I think Dr. Castleman is now referring to an interesting case of hypernephroma[4] with a single bone metastasis to the pelvis. The blood chemical findings (a high serum calcium, a low serum phosphorus and a normal serum protein) were most suggestive of hyperparathyroidism. We sent some tumor tissue obtained at autopsy to Dr. Collip to see whether it contained parathyroid hormone. It did not.

DR. PHILIP HENNEMAN: The occasional occurrence of hypercalcemia in certain malignant tumors without bony metastases is an enigma. Stewart and Bowen[5] have recently reported that properly prepared extracts of thymus and spleen are capable of inducing a phosphate diuresis. If these data were confirmed they would lend support to the possibility that these actively growing tumors would simulate hyperparathyroidism by inducing a phosphate diuresis with ensuing depression of serum phosphate and elevation of serum calcium levels.

DR. BAUER: What were the final diagnoses?

DR. CASTLEMAN: Hemangiosarcoma of the liver, with metastases to the adrenal gland, and hypercalcemia, cause entirely unknown.

DR. BAUER: It is too bad that you did not find the fourth parathyroid.

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CASE 39062

PRESENTATION OF CASE

A sixty-two-year-old woman entered the hospital because of pain in the back of the neck and weakness of the left arm and leg.

The patient was well until about four months before admission, when she noted that her legs jerked spasmodically at night, the left perhaps more severely than the right. This became progressively worse. Three weeks before entry she began to have pain in the back of the neck, radiating to both shoulders, and a progressively developing weakness of the left arm, most marked in the hand, and of the left leg. At the onset of the weakness, there was "numbness" of the left arm and hand that disappeared shortly thereafter. She was able to walk, but with considerable unsteadiness, and had recently fallen down and bruised herself. One week before admission for a period of

three days she noted a desire to void frequently but could only pass small amounts of urine. She had not been incontinent of urine or feces. A lumbar puncture at another hospital two days before admission showed dark, bile-colored spinal fluid under a pressure equivalent to 40 mm. of water that did not rise on jugular compression. The fluid contained a "very high protein" and 100 white cells and 30 red cells per cubic millimeter.

She stated that she had always had a tendency to bruise easily. The past history was otherwise noncontributory.

Physical examination revealed a well developed woman who appeared pale, drawn and chronically ill but was not emaciated. The heart and lungs were not remarkable. Many ecchymoses were present over the back of the legs and thighs. There was marked tenderness over the lower two cervical and upper two thoracic vertebras. Marked weakness of the left triceps and extensors of the left wrist and fingers was present, with good but not normal strength in abduction of the left shoulder and flexion of the left elbow. The intrinsic muscles of the left hand were moderately weak. The right upper arm was normal. Both legs were weak, the left more so than the right; she could barely move the toes of the left foot; both legs could be passively raised to 90° without discomfort. Muscle tone was normal in all four extremities. The tendon reflexes in the arms and the knee jerks were abnormally brisk, and equal. The ankle jerk was moderately active on the right and weak to absent on the left. Abdominal reflexes were absent. The plantar reflexes were indefinite or extensor bilaterally. Pain and light-touch sensations were decreased below the level of the second rib on the left and the third rib on the right. There was no impairment of proprioceptive sensations except possibly in the left great toe.

The temperature was 98.6°F., the pulse 80 and the respirations 20. The blood pressure was 150 systolic, 95 diastolic.

The urinary sediment contained 8 white cells and a rare hyaline cast per high-power field. Examination of the blood revealed a hemoglobin of 15.1 gm. and a white-cell count of 9000, with 79 per cent neutrophils; the blood platelets and red cells were normal. The prothrombin time was 13 seconds (normal, 14 seconds), and the bleeding time three minutes; the clotting time and the clot retraction were normal. The total protein was 6.5 gm. per 100 cc. A test for Bence-Jones protein was negative. Hinton tests on the blood were reported positive on two occasions and negative once; simultaneous Wassermann reactions done on duplicate samples were negative. The cerebrospinal fluid obtained at myelography was dark yellowish brown (coffee colored), and contained 4150 mg. per 100 cc. of protein. The cell count (rendered inaccurate by rapid clotting of the fluid) was 43 lymphocytes and 2 neutrophils per cubic millimeter.

Roentgenograms of the chest disclosed a kyphosis of the dorsal spine, with increase in the anteroposterior diameter of the chest. The peripheral lung fields were clear. The heart was not enlarged. The aorta was elongated and tortuous. X-ray films of the abdomen showed calcification of the aorta and pelvic vessels. A soft-tissue mass in the pelvis suggested a distended bladder.

A myelogram demonstrated complete obstruction to the upward flow of contrast material at the

FIGURE 1.

fifth thoracic vertebra, with a cup-like defect in the radio-opaque column opposite the obstruction (Fig. 1). With the patient standing, there appeared to be another defect opposite the first sacral vertebra, with a rather sharp cut off of the column at this level.

In the hospital the patient was unable to void when on the bedpan, but otherwise showed no clinical changes initially. On the third hospital day laminectomy and spinal-cord decompression extending from the seventh cervical to the third thoracic vertebra were performed. The patient did well immediately after the procedure, moving both legs fairly well; however, she was put on tidal drain-

age because of complete urinary retention. The early postoperative course was otherwise uneventful, except for some drowsiness, which appeared on about the third postoperative day. After about two weeks, the drowsiness became more severe, and on the seventeenth postoperative day, she became semistuporous, responding only briefly to insistent questioning. The left pupil and then both pupils became dilated, but reacted to light. The disk margins were blurred, and there was a divergent strabismus, with a full range of ocular movements. Plantar reflexes were extensor bilaterally. A few hours later she suddenly became cyanotic and comatose, and spontaneous respirations ceased. She lived a few more hours in a respirator, dying on the eighteenth postoperative day.

Differential Diagnosis

Dr. Bertram Selverstone*: May I see the x-ray films?

Dr. James J. McCort: The chest films are normal, except for a slight prominence of the left ventricle and a tortuous aorta, which is compatible with a slight degree of hypertension.

The films of the dorsal spine show slight demineralization of the bone, which is not unusual at the patient's age. There is no evidence of bone erosion or destruction. The pedicles are intact, and the interpediculate spaces are not widened. In the plain film of the abdomen the liver and the spleen are of normal size; the kidneys are obscured by the intestinal contents. A soft-tissue mass in the pelvis seems to represent a distended urinary bladder. There is calcification of the abdominal aorta and pelvic vessels. No abnormal abdominal masses are seen.

In the myelographic films taken with the patient's head lowered, the oil column at the fifth dorsal vertebra shows complete block and a cup-like defect (Fig. 1). With the patient erect, there is a cut off at the level of the fifth lumbar and first sacral interspace. The defect at the level of the fifth dorsal vertebra is quite definite and represents complete block. The defect at the fifth lumbar vertebra is somewhat questionable; this type of defect could be caused by spondylolisthesis or posterior spurring, the possibility of which is easily excluded on a lateral film.

Dr. Selverstone: This patient presents two seemingly distinct problems; at least, I should prefer to divide the case into preoperative and postoperative diagnostic problems.

In summary, the history is one of progressive spinal-cord compression in the lower cervical and upper thoracic regions for about four months. Later there were meningeal and root pain, numbness in the left upper limb, which was apparently transient, weakness of both lower limbs, which persisted, and temporary difficulty with the bladder, which improved somewhat before admission to the hospital.

There was local tenderness from the spine of the sixth cervical to that of the second thoracic vertebra. Weakness was present in the left upper limb, exhibiting a segmental pattern, with the fifth cervical segment normal, the sixth slightly involved, the seventh and eighth markedly involved and the first thoracic segment only slightly impaired. It would be interesting to know if there were fasciculations or electromyographic changes that would confirm this segmental pattern. The tendon reflexes were increased in both upper extremities, including the triceps reflex, indicating pyramidal involvement above this level. The abdominal reflexes were absent, and the plantar reflexes abnormal. There was weakness of both legs, the left more than the right. The ankle jerks were unusually depressed for such a lesion as this, especially the left, which was apparently almost absent. One wonders about a possible correlation with the sacral cut off that was seen in the myelogram. There was a partial spinothalamic-tract level at the second or third thoracic vertebra, with relative preservation of function of the posterior column.

The cerebrospinal fluid presented a most unusual appearance — one that cannot be explained simply by the high protein or as extreme xanthochromia, since the fluid was described as "dark, bile-colored" on one occasion and as "coffee colored" on another. Such changes in color are never seen simply with a subarachnoid block. There were 70 red cells and 100 white cells per cubic millimeter in the fluid from the first lumbar puncture and later 43 white cells, chiefly lymphocytes. There was myelographic evidence of an obstruction at the fifth thoracic vertebra. When we add to this our clinical data, we have evidence for a long lesion, extending from the sixth cervical to the fifth thoracic level. Furthermore, there is what is classically described as the "capping" of an extramedullary lesion in the myelogram. Would you agree with this, Dr. McCort?

Dr. McCort: Capping frequently indicates an extramedullary intradural lesion, but we have not found it invariably reliable.

Dr. Selverstone: There was, then, a long lesion extending over six or seven vertebras, a complete block, the possibility of a second lesion at the sacral level and a most extraordinarily colored cerebrospinal fluid containing 43 lymphocytes and 2 neutrophils per cubic millimeter.

When considering the common obstructing lesions of the spinal canal, I think first of extramedullary intradural tumors — neurofibroma, perineurial fibroblastoma and meningioma. These are short tumors in general, rarely extending over more than two vertebras. Neurofibromas may be multiple, of course, but here I should have to postulate a veritable cluster of neurofibromas extending over many

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segments together, with another at the sacral level. The strange color of the cerebrospinal fluid would not be explained by neurofibroma.

Metastatic carcinoma or myeloma may be extensive and may compress the dura over long distances. There are no bony changes in the x-ray film consistent with these, and no evidence of metastatic disease in the x-ray examination of the chest. As far as myeloma is concerned, there was no evidence of Bence–Jones protein. These neoplastic lesions, too, would not explain the strange color of the cerebrospinal fluid, which I must take to have some importance; metastases are usually extradural, and it would be unusual for an extradural lesion to produce such a pronounced change in the color of the cerebrospinal fluid.

A meningeal sarcoma can be long and can be hemorrhagic. It would explain the color of the fluid on the basis of blood pigment. It can implant to form a second lesion at a lower level. I cannot rule it out even in the absence of bone changes — there may be no bone changes with a meningeal sarcoma.

Intramedullary tumors may extend over many segments, but at the level of the brachial plexus, with such marked motor involvement of the left upper limb, there should almost certainly be sensory changes in the left or in both arms — perhaps even dissociation, although one cannot depend on that. With an intramedullary tumor, I should have said that so unusual a color of the cerebrospinal fluid would not have been at all likely, had I not recently operated on such a patient, whose cerebrospinal fluid was colored almost as deeply as that described here. I think the myelographic appearance, although not always reliable, as Dr. McCort says, is against an intramedullary tumor. I am at a loss also, on the basis of an intramedullary tumor, to explain the myelographic cut off at the first sacral level.

The same arguments concerning intramedullary tumor apply to syringomyelia and hematomyelia, but with even more force, since dissociated sensory loss in the arms would probably be present. Total blockage of this degree would be unusual with such a short history, and the color of the cerebrospinal fluid would be most unusual even with hematomyelia.

I must consider, in the diagnosis of a long lesion, an inflammatory process such as extradural granuloma, usually the result of a sluggish staphylococcal infection. The lymphocytosis in the spinal fluid is consistent with such a lesion. But there was no history of an antecedent infection, no fever and a normal white-cell count in the blood, with only a slight rise in neutrophils. And here again, as with any extradural lesion, the strange color of the cerebrospinal fluid remains unexplained.

I must mention hypertrophic cervical pachymeningitis, but that is a much more chronic disease, with symptoms usually extending over a period of years; the remarks concerning the cerebrospinal-fluid color and the questionable sacral lesion also apply here.

Syphilis must be mentioned, since there were equivocal serologic changes in the blood. Granulomas can occur, but probably not with serologic findings only equivocally abnormal.

A disease that we are seeing with increasing frequency — chronic cystic arachnoiditis — should be mentioned, but here again the history is usually much longer. This patient apparently had no history of spinal medication or anesthesia. The degree of block would be unusual, and again the deep color of the cerebrospinal fluid would be unexplained.

I am being forced farther and farther afield, and have eliminated the conditions that this ought to be. I am forced again to something that I may be overemphasizing: the fact that the cerebrospinal fluid was said to be the color of bile on one occasion and of coffee on another. These are not colors that are often seen in the cerebrospinal fluid, and I am forced to conclude that the color was caused in some manner by the presence of blood pigment. A rare lesion to consider is a more or less encapsulated intradural hemorrhage in the lower cervical and upper thoracic region, which could be long, extending over several segments, could compress the left anterior column or anterior roots and thus produce the segmental findings in the left upper extremity and could also compress the spinal cord, causing the long tract signs. One considers the attractive but perhaps farfetched possibility that such a hemorrhage leaked through a tear in the delicate arachnoid and, since the patient was ambulatory, gravitated in the canal, as in a sedimentation tube, to form a sacral lesion in the myelogram.

How am I to explain such a hemorrhage in the absence of a history of trauma? I have mentioned hemorrhagic dural sarcoma, which could implant and produce a sacral lesion below, without implicating a sedimentation process. The absence of bone changes does not rule it out, although it is against it. A vascular malformation or aneurysm could also be responsible for such a hemorrhage. Against that possibility, but certainly not ruling it out, is the fact that these lesions usually have a chronic course, with exacerbations and remissions over a period of years before the onset of a catastrophic event such as this. I must consider a blood dyscrasia. The patient always bruised easily, and when she was admitted to the hospital she had ecchymoses on the thighs and legs, but the bleeding time, the clotting time, the clot retraction, the platelet count and the prothrombin time were normal. These do not completely rule out an abnormality of bleeding, but they exclude the more common abnormalities. I think that I must stand somehow on the diagnosis of a long lesion produced by a chronic

organizing hematoma within the dura. I cannot completely rule out an intramedullary tumor.

I am now ready to be seated, but find that I have what amounts to another case to discuss, the cause of this patient's death on the eighteenth day after laminectomy. Here I come to a whole new set of symptoms, none of which were present before. I must discuss it with fewer data than I should like to have. I do not know the values of the blood electrolytes, the x-ray findings in the skull, including the question of pineal shift, the results of electroencephalography or the lumbar-puncture findings. From the data at hand, however, there was evidence of increasing intracranial pressure: there was drowsiness progressing to stupor; there were oculomotor signs both in the pupils and in the presence of divergence; and there was blurring of the disk margins. Blurring of the disk margins may be within normal limits, but when it is mentioned for the first time one must assume that the disks were normal before operation and that the blurring represented early papilledema. I cannot interpret the plantar reflexes, which were said to be extensor, because of the presence of a spinal lesion. I do know that this was a respiratory death, the sort of death one would expect with increasing intracranial pressure. There were no bulbar symptoms mentioned, no nystagmus, so that the findings are not particularly suggestive of the upward extension of an intramedullary lesion into the posterior fossa.

The possibility I shall consider is merely a guess, since I must make a diagnosis. In the course of laminectomy, especially when the head is higher than the rest of the body, there is often a sudden loss of cerebrospinal fluid, which produces a dislocation of the brain by gravity and may cause a tear of a bridging vein to the superior longitudinal sinus. The resultant subdural bleeding may become encapsulated and by osmosis and transudation act as a space-taking intracranial lesion. This is a far-fetched possibility, but one that has been reported, and is the only correlation that comes to mind with the patient's previous history. The only evidence of lateralization of such a putative hematoma is the early enlargement of the left pupil. Of course, a hematoma may be, and in many cases is, bilateral. As a guess I shall postulate a chronic intracranial hematoma as the cause of death.

Clinical Diagnosis

Extradural malignant neoplasm.

Dr. Bertram Selverstone's Diagnoses

Subdural hematoma of spinal cord.
Subdural hematoma of brain.

Anatomical Diagnosis

Meningomyelitis and encephalitis, chronic, syphilitic.

Pathological Discussion

Dr. William H. Sweet: The patient's physician was the first one to draw attention to the extraordinary appearance of the spinal fluid. At operation we were quite bewildered by the findings; on opening of the dura the arachnoid was materially thickened and contained mottled reddish masses of tissue. These masses were not adherent to the cord proper so that the arachnoid could be dissected off the pia fairly readily over quite a wide area. A biopsy of this was diagnosed in frozen section in such a fashion as to make us desist from further operation, so that we did not remove all the diseased tissue.

Dr. Lawrence Barrows: Did you run a bilirubin test on the spinal fluid?

Dr. Sweet: The fluid was examined spectroscopically by Dr. Francis T. Hunter and showed the characteristic absorption lines of methemoglobin — a pigment that one would expect to see here only if hemorrhage had previously been present.

Dr. Edgar B. Taft: At autopsy there were no abnormal findings in any of the organs except the brain and spinal cord, which will be discussed by Dr. Richardson.

Dr. Edward P. Richardson, Jr.: This was a most unusual and puzzling case. The frozen section of the tissue that Dr. Sweet encountered at operation showed for the most part sheets of large cells with vesicular nuclei that were thought to be consistent with an undifferentiated malignant tumor, and that opinion was reported to Dr. Sweet. A few mononuclear inflammatory cells were seen, but not much attention was paid to them. When permanent sections had been prepared, it was apparent that the inflammatory aspect of this lesion was the significant one. There were many lymphocytes and plasma cells, and the large cells that we had seen on frozen section turned out to be not neoplastic cells but arachnoid cells. At post-mortem examination there was such extensive thickening of the pia arachnoid that the spinal cord itself could not be seen at all in the cervical and upper thoracic regions, except where Dr. Sweet had removed some of this tissue. The dura mater in this region was likewise thickened, and was adherent to the arachnoid. The thickening gradually tapered off from about the midthoracic level down and was not at all pronounced in the lumbosacral region of the cord. This thickening of the arachnoid was also present over the medulla oblongata, the pons, the cerebellum and, to a lesser extent, the base of the brain. There was only insignificant meningeal thickening over the convexities of the cerebral hemispheres.

Microscopical examination demonstrated that we were dealing with a chronic granulomatous meningitis, characterized by a profuse exudate in which the predominant cell in many areas was the plasma cell. In addition there were numerous

lymphocytes, occasional foreign-body giant cells and, where the exudate was thickest, some red blood cells. Along with this copious cellular exudate there was an extreme degree of fibroblastic proliferation in the meninges, which was another prominent feature of this inflammatory reaction. Arachnoid cells, normally found only in small clusters, had proliferated to such an extent in the cervical and upper thoracic regions that they formed a continuous layer. At all levels of the central nervous system, inflammatory cells were seen in the adventitia of the blood vessels, and there was fibrous thickening of the walls of many small meningeal

FIGURE 2. *Cervical Spinal Cord (Myelin Stain).*

and parenchymatous arteries, producing a typical endarteritis obliterans. These vascular changes were most prominent at the levels of the brain stem and spinal cord, but were present in sections from the cerebral cortex as well.

Within the central nervous system itself, the most severe changes were in the spinal cord and lower medulla oblongata, where the meningeal involvement was most marked. At these levels, there was a peripheral zone of total destruction of nerve fibers that completely encircled the neuraxis (Fig. 2). The penetrating vessels passing through this region were variably thickened and were frequently accompanied by perivascular inflammatory cells similar to those in the meninges. The structures in the center of the cord and brain stem were relatively better preserved, but there was widespread astrocytic and microglial proliferation, and many nerve cells had disappeared. There was a severe granular ependymitis of the walls of the third ventricle and cerebral aqueduct and the floor of the fourth ventricle. There were likewise foci of destruction of brain tissue in the outermost folia of the cerebellum, underlying the thickest accumulations of meningeal exudate, and in the periphery of the midbrain. Compared with the brain stem and spinal cord, the cerebral cortex and central gray nuclei of the brain were relatively intact. However, perivascular inflammatory infiltrations were frequent in these regions, and in some sections of cerebral cortex, there were numerous striking rod-shaped microglial cells.

We were unable to demonstrate a causative organism, despite appropriate cultures and staining methods. The pathological findings, however, are typical of chronic syphilitic meningitis, and do not fit in well with any other condition. The proliferative inflammatory reaction, the vascular changes and the exudate containing many plasma cells are all indicative of this disease. Confirmatory is the finding of a positive blood Hinton test. The central-nervous-system changes may be considered to be secondary to this severe meningovascular inflammation.

DR. MADELAINE R. BROWN: Was the lesion at the fifth lumbar vertebra the same?

DR. RICHARDSON: We could not be certain at post-mortem examination of obstruction to the cerebrospinal-fluid pathway at that level, but overlying the lumbosacral spinal cord and cauda equina there was the same chronic meningitis that was present elsewhere although the meningeal thickening was not as marked at these lower levels.

DR. SWEET: I think it might be worth emphasizing that the gross appearance was exceedingly unusual. Neither Dr. Richardson nor I had ever seen anything like this before. The abnormal appearance of the arachnoid completely bewildered us in both its gross and its microscopical appearance. In fact the picture was so unusual that when the brain and spinal cord were cut at the time of the full post-mortem examination nobody had any clear-cut idea of exactly what this lesion was.

Evaluation of Clinicopathological Conferences. To evaluate the place of the clinicopathological conference in medical education, Dr. Castleman would like to obtain a list of the groups that use the Massachusetts General Hospital Case Records as a teaching exercise in their society or hospital meetings, dinner clubs, student conferences and so forth. Replies indicating the method used in the group should be made directly to Dr. Castleman, Massachusetts General Hospital, Boston 14. Comments and suggestions will be welcome.

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THERAPEUTIC EXUBERANCE

As Finland and Weinstein emphasize, it would be a gross misinterpretation of the purpose of their communication, published elsewhere in this issue of the *Journal*, to conclude that antibiotic agents do more harm than good. Perhaps the main contribution of this review will be clearest to practitioners whose experience antedated the sulfonamide era and who became familiar with and appreciative of the natural recuperative powers of the human body unaided in its struggle against microbial invaders. Many of these had arrived at a judicious attitude of "therapeutic nihilism," the basic tenet of which was to avoid doing harm to the struggling organism when the medical pharmacopoeia was known to be ineffective; if they could not cure arthritis, they at least recognized their responsibility not to make the patient sicker by trying to do something on an unscientific basis. Meanwhile, he could be treated symptomatically.

The nihilists were not unreasonably skeptical and were neither the first to lay the old aside nor yet the last to try topical, intravenous, parenteral and serum therapy as one by one such useful agents were added to the effective armamentarium of the physician.

The new era ushered in by the advent of Prontosil, however, spelt the end of anything resembling "therapeutic nihilism." The situation had changed gradually during the days of serum therapy, but henceforth, there seemed little place for mere ministering to bodily comfort while the body fought out its own kind of biologic warfare. More important, the advent of sulfonamides and antibiotics meant that subsequent generations of practicing physicians would hardly know how accustomed their predecessors were to see patients with acute infectious disease quietly recover with no specific treatment. The oldfashioned nihilists knew how easy it would be for those of the younger generation to believe that they had won all the victories with their newly emerging battery of wonder drugs. It was not that the newer generation would be less honest or less exacting than its elders, but it would have no standard of reference; its conceit would be scrupulous and natural.

Now comes the admonition by Finland and Weinstein that the old timers had, and still have, a healthy point of view, and that the physician still has his first responsibility of not doing more harm than good. Nihilism, as a reasonably sound approach to the care of the sick, has presumably gone forever, but the physician must still study his own limitations, the patients' own role in victory and the risks of therapy as well as its benefits. The antibiotics are revealed, as the experienced therapist has known them for years, as agents to be employed when the battle is critical or fraught with risk, but neither a substitute for natural resistance and acquired immunity nor a new invention outmoding the necessity for medical judgment.

THE PRINTED WORD

A YEAR or two more or less in a period of approximately five centuries makes little difference one way or the other as time is reckoned, so it is not inappropriate that a special three-cent stamp should have been issued in 1952 to commemorate the five-hundredth anniversary of the printing of the Gutenberg Bible. Whether or not 1452 was the actual year of the publication is a matter on which the encyclopedias cautiously refrain from committing themselves, preferring to set the time somewhere between 1450 and 1456.

The important and appropriate fact is that the Book of Books should have been the first of man's writings to have been put into print and released to the world by means of this revolutionary press with its movable type. For by its very name the Bible is identified as the book of first importance, its title having been derived from the Latin *biblia*, treated as singular although representing the transcription of the Greek neuter plural *biblia*, or little books, coming in turn from *byblus* or papyrus. "The name in its singular form emphasizes the unity of the Bible, while in its original plural sense it calls attention to the fact that the Bible is a collection of many books."

The writing of the Bible having been the work of many hands, it is fitting that its printing, too, should have been a co-operative effort and that so important a discovery as that of printing should not be attributable to one man alone. Not only did the Chinese print by hand with block type before the birth of Christ, but Laurens Coster, of Haarlem, is credited with having printed a book about 1438, and it is a matter of record that Johannes Gutenberg was greatly aided in his work by Peter Schöffer's invention of the necessary punches and matrices. The development of a suitably viscous ink, attributed to Coster, also played no small part in the success of printing.

Only three perfect copies of the Gutenberg or Mazarin Bible are known to exist, the finest of which is in the Library of Congress, at Washington. The determination of the finest of three specimens of perfection is best known to the editors of Funk and Wagnalls *New Standard Encyclopedia*, who are responsible for the comparison. The name of Cardinal Mazarin became associated with Gutenberg's 42-line Bible at a later time, when it was discovered in his library, for Mazarin was not born until a hundred and fifty years after the publication of the famous work.

The relation of this semimillennium of practical printing to the profession of medicine is the same that it bears to any of the learned professions or any of the world's cultures. For it is through this making available of the records of discovery and the spreading of the word that progress has been able to keep up the accelerated pace set by the rebirth of intellectual curiosity in the fourteenth and fifteenth centuries. Books on medicine were among the earliest printed, after the Bible; and of medical incunabula, or works published in the cradle period of printing, before 1500, the Boston Medical Library has one of the world's finest collections.

Of the widening stream of literature and particularly, to the *Journal's* readers, of medical literature, that grew from this original source with its clear currents and countercurrents, its backwaters and its flotsam and jetsam, much has already been written.

WRONG DIAGNOSIS

THE difficulties, in which a number of Jewish physicians of Moscow recently found themselves have aroused the sympathies of the civilized world. Accused of terrorism in plotting to remove from circulation certain top brass Russian political and military leaders, they were alleged to have worked under orders from an international Jewish bourgeois-nationalist organization established by the American Intelligence Service. This organization is presumably the American Jewish Joint Distribution Committee, a philanthropic agency known in Europe as "Joint." The Bolsheviks, with their customary amiability, are apparently aching to announce that the Joint is pinched.

The nine physicians arrested were said to have confessed to the assassination of Andrei A. Zhdanov, high-ranking member of the politburo who died in 1948, and of abbreviating the terrestrial existence of one Alexander S. Scherbakov, head of the chief political administration of the Soviet Army, who shuffled off this mortal coil in 1945.

According to a broadcast relayed through the Associated Press from Tass, the official Soviet news agency, the criminals concealed Mr. Zhdanov's true diagnosis of myocardial infarction, prescribed a contraindicated treatment and thereby maliciously destroyed Comrade Zhdanov. In the case of Mr. Scherbakov the same physicians "incorrectly applied strong medicines for his treatment, introduced an experimental regime and thus caused his death."

Throughout history reigns of terror have eventually consumed themselves. Meanwhile one can but ask, "How long, O Lord, How long?"

ADRENAL STEROIDS — RESEARCH AND THERAPY

THE Medical Progress report in this issue of the *Journal* is the first instalment in a series covering advances in research and therapeutic applications of ACTH, cortisone and related steroid hormones. The series, which will be concluded in a March issue, represents exhaustive work on the part of the authors, Dr. George W. Thorn and his associates at Harvard Medical School and the Peter Bent Brigham Hospital, who have attained the position of authorities on the experimental and clinical uses of these substances.

In devoting a number of issues to the presentation of this subject the editors have been guided not only by the wide interest in the adrenal steroids and their applicability to many fields of medical practice but also by the valuable data presented. The articles constitute, in effect, a monograph on the advances made in this field, covering the entire subject in authoritative terms. The *Journal* is confident that the series will prove of interest and value to specialists in such diversified fields as endocrinology, cardiology and surgery, as well as to those whose practice is limited only by the confines of the healing art.

Died. — At Astoria, N. Y., Dr. Junius Smith, the first to introduce the growing of tea in America. He was a man of great energy and enterprise.

Boston M. & S. J. *February 9, 1853*

CORRESPONDENCE

PERMANENTE PLAN

To the Editor: It was surprising to read the editorial in the October 30 issue of the *Journal*, which was so laudatory to the Permanente Plan. It is obvious that no real study of the plan was made, nor any attempt to hear the other side.

I am certain that a majority of the members of the San Francisco Medical Society would not agree with your comments.

GEORGE K. HERZOG, JR., M.D.

San Francisco

BOOK REVIEWS

Psychotherapy of Psychosis. By Gustav Bychowski, M.D. 8°, cloth, 328 pp. New York: Grune and Stratton, 1952. $5.75.

The work of Dr. Bychowski in psychotherapy of schizophrenia is a comprehensive study of the various dynamic factors involved in the schizophrenic process and other psychoses, with particular attention to the psychotherapeutic relation that can be established between the therapist and the patient. His entire discussion is psychoanalytically oriented, and the psychopathology is therefore discussed primarily from that point of view. This volume is a valuable adjunct to any psychiatric library.

HUBERT A. CARBONE, M.D.

The Case Against Psychoanalysis. By Andrew Salter. 12°, cloth, 179 pp. New York: Henry Holt and Company, 1952. $2.50.

The purpose of this volume is clearly defined in the title. The contents are an expression of the author's impatience and disagreement with the psychoanalytic school of thought. It is written primarily for the layman whose knowledge of Freudian theory is superficial and limited. It is quite obvious that the author directs this book toward this type of reader since he goes to great pains to oversimplify and to define terminology that might otherwise be obscure. The author points out repeatedly that the desire of the psychoanalyst to be considered scientific is not borne out by what he considers to be the facts of the case. He repeatedly points with an accusing finger to many inconsistencies and discrepancies and purely subjective interpretations of psychoanalysis.

This work has value in the sense that it may cause some readers to attempt to evaluate more objectively some of the statements made by psychoanalysts. However, it is unfortunate that the author's own emotional reaction to this concept should so color his writing. Perhaps a more objective evaluation would have been of greater value. The author cites various examples and cases particularly designed to ridicule many of the "fantasies" of the Freudians. He honestly expresses his belief that psychoanalysis is not only invalid but can produce (and has produced) more harm than good.

In summary, the author's case against psychoanalysis is expressed in firm and sometimes emotional language, but no complete evaluation of the psychoanalytic theory is given.

HUBERT A. CARBONE, M.D.

The Auricular Arrhythmias. By Myron Prinzmetal, M.D., Eliot Corday, M.D., Isidor C. Brill, M.D., Robert W. Oblath, M.D., H. E. Kruger, and associate authors. 4°, cloth, 398 pp., with 514 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $16.50.

This attractive volume is not a textbook of the auricular arrhythmias — rather, it is an account of the well known experimental work being done by the authors to refute the classic theories of production of auricular flutter and other arrhythmias. Using the new tools of high-speed moving-picture camera, and cathode-ray electrocardiograph, the authors have disproved in convincing fashion the circus-wave theory of Thomas Lewis. The experimental proof of the authors is quite convincing, representing an extension

of work begun by Scherf and others. Illustrations and photographs in black-and-white and in color are excellent.

The book is recommended to those who have special interest in the field of electrocardiography.

CONGER WILLIAMS, M.D.

The Drawing-Completion Test: A projective technique for the investigation of personality based on the Wartegg test blank. By G. Marian Kinget, Ph.D. With a foreword by Percival M. Symonds, Ph.D. 4°, cloth, 238 pp., with 162 illustrations. New York: Grune and Stratton, 1952. $6.75.

In this book the author sets herself the ambitious task of introducing a new projective technic, presenting its historical background and development, outlining validation procedures and discussing methods of administration, scoring and interpretation. Her conclusions are based on research carried out on a group of 383 "normal" adult subjects who were given the Drawing-Completion Test as well as three "objective" tests of personality. The test itself consists of eight simple graphic elements, each of which the subject is requested to develop into a drawing. These drawings constitute the raw material from which the structure and function of personality, as well as any psychopathology, are derived. The areas investigated — emotion, imagination, intellect, control and reality function — are strikingly parallel to those of the Rorschach test.

Workers in the field of personality investigation might well regard with a critical eye the appearance of another projective technic in this rapidly expanding field. The questions that arise most readily are, What particular advantages does this technic have and in what way does it supplement existing methods? As far as the former is concerned, the Drawing-Completion Test has obvious advantages from a practical point of view in that it does not require the presence of the examiner throughout its administration, and is relatively independent of verbal ability and language barriers. Unfortunately, the second question cannot be dismissed so easily. Not only is new material lacking but also the test falls short of older technics in certain respects. Although its applicability in psychiatric diagnosis is broadly hinted at, no clinical material appears in the book to support such a point of view. This may be due, in part, to the author's manner of presentation rather than a shortcoming of the test itself, since only a relatively small portion of the book is given over to the actual interpretation of sample records. Instead, the abundant inclusion of illustrative material serves as a point of departure for discussions of scoring. Furthermore, one feels a lack in that even the limited number of sample interpretations are not supplemented with personality data obtained from other sources. In the final analysis, of course, the Drawing-Completion Test will stand or fall on the basis of its usefulness in practice. And, so far as the book constitutes a manual for the use of this test, it should serve adequately as a starting point for those who are interested in subjecting the technic to the ultimate criterion.

MARGARET B. SCALES, M.A.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Accelerated Conduction: The Wolff–Parkinson–White syndrome and related conditions. By Myron Prinzmetal, M.D., Rexford Kennamer, M.D., Eliot Corday, M.D., John A. Osborne, M.D., Joshua Fields, M.D., and L. Allen Smith, M.D. 8°, cloth, 110 pp., with 48 illustrations. New York: Grune and Stratton, 1952. $4.00. (*Modern Medical Monographs.*)

This monograph presents the results of a series of experimental investigations of the Wolff–Parkinson–White syndrome and a complete survey of the literature. The first comprehensive description of the syndrome was made in 1930 by Dr. Louis Wolff, Sir John Parkinson and Dr. Paul D. White, with a review of 11 cases. Accelerated conduction and the clinical significance of both the nodal and ventricular types are discussed at length. There is a bibliography of 66 references and an index. The small book should be of interest to cardiologists.

Introduction to Clinical Neurology. By Gordon Holmes, M.D., F.R.S. Second edition. 8°, cloth, 189 pp., with 43 illustrations. Baltimore: Williams and Wilkins, 1952. $4.00.

The first edition of this book was published in 1946. In this new edition the author has made few changes. Some additions have been made to the material on the functional organization of the higher levels of the motor system and on the hypothalamus. The printing was done in Great Britain.

Über den Wahn. By Kurt Schneider, professor, Universität Heidelberg. 8°, paper, 48 pp. Stuttgart: Georg Thieme, 1952. Kart. DM 3.90. (Distributed by Grune and Stratton, New York.)

This small monograph discusses the comprehensive and clinical aspects of hallucinations.

Practical Pharmacology. By J. H. Burn, professor of pharmacology, University of Oxford. 8°, cloth, 72 pp., with 43 illustrations by E. M. Vaughan Williams. Oxford, England: Blackwell Scientific Publications, 1952. (Distributed by Charles C Thomas, Springfield, Illinois.) $3.25.

This manual presents 21 experiments for students on the effects of pharmacologic preparations on isolated muscles of various types. The book is published simultaneously in the United States by Charles C Thomas.

Hemifacial Spasm: A clinical and pathophysiological study. By Robert Wartenberg, M.D. With a foreword by Macdonald Critchley, M.D. 8°, cloth, 86 pp., with 25 illustrations. New York: Oxford University Press, 1952. $4.00.

Dr. Wartenberg, originally with the University of Freiburg, is now with the University of California, where he is conducting investigations in clinical neurology. A careful study has been made of the disease, and the literature has been surveyed. The theory that hemifacial spasm is a release phenomenon is discussed in detail. There is a bibliography of nearly 7 pages, and 27 full-page illustrations. The monograph should be in all collections on neurology.

Elementary Medical Statistics: The principles of quantitative medicine. By Donald Mainland, M.B., Ch.B., D.Sc., F.R.S.E., F.R.S.C., professor of medical statistics, Division of Medical Statistics, Department of Preventive Medicine, New York University College of Medicine. 8°, paper, 327 pp., with 23 illustrations and 5 tables. Philadelphia: W. B. Saunders Company, 1952. $5.00. (*American Monograph Series.*)

Dr. Mainland presents the elements of statistics and their place in medicine. One chapter discusses statistical ideas in clinical medicine, pointing out normal values, possible errors and fictitious figures. The book is published in an inexpensive manner and is recommended as a reference source for medical libraries.

Die Vorträge der 2. Lindauer Psychotherapiewoche 1951. Edited by Doz. Dr. Ernst Speer. 8°, paper, 216 pp. Stuttgart: Georg Thieme, 1952. Kart. DM 15.–(Distributed by Grune and Stratton, New York.)

This volume comprises the transactions of the second Lindauer conference on psychotherapy held in 1951. Twenty-two pages on various aspects of the subject were read during the week. The publishing is good, and the volume should be in all collections on the subject.

Surgical Technique. By Stephen Power, M.S., F.R.C.S., senior surgeon to the Dreadnought Hospital, Greenwich, surgeon to the Royal London Homoeopathic Hospital, and surgeon to Eltham Hospital. 12°, cloth, 380 pp., with 198 illustrations. Philadelphia: J. B. Lippincott Company, 1952. $6.50.

This manual, designed for the young surgeon, presents procedures usually omitted from standard textbooks. The text is concise and well written. The printing, which was done in Great Britain, is excellent. The small book should prove valuable to surgeons.

Surgical Forum: Proceedings of the forum sessions, thirty-seventh clinical congress of the American College of Surgeons, San Francisco, California, November 1951. 8°, cloth, 667 pp., with 290 illustrations. Philadelphia: W. B. Saunders Company, 1952. $10.00.

This volume of transactions covers the whole field of surgery, general and special. It is well published and should be in all medical libraries.

Medizinische Röntgentechnik, in zwei Teilen. Physikalisch-technischer Teil: 1. *Grundlagen der Strahlendiagnostik und Strahlentherapie, Apparatekunde.* 2. *Röntgen- und Farben-photographie.* By Dipl.-Physiker Erich Bunde, Karlsruhe, and Dr. Viktor Loeck, Wuppertal-Elberfeld. 8°, cloth, 360 pp., with 217 illustrations. Stuttgart: Georg Thieme, 1952. Ganzleinen DM 27.– (Distributed by Grune and Stratton, New York.)

The second part of this work on medical roentgenology is devoted to the physical and technical aspects of the subject. The text is divided into two sections: the fundamentals of diagnosis and treatment; and roentgen-ray and color photography. There is a comprehensive index for the two volumes. The publishing is excellent. The complete work should be in all collections on radiology.

Tuberculosis of Bone and Joint. By G. R. Girdlestone, and E. W. Somerville, M.B., F.R.C.S.(Ed.), orthopedic surgeon to the Winfield-Morris Orthopaedic Hospital, Oxford. Second edition. 8°, cloth, 314 pp., with 182 illustrations. New York: Oxford University Press, 1952. $8.75. (From the Nuffield Orthopaedic Centre; *Oxford Medical Publications.*)

The authors have revised the text of this special book, first published in 1940. Material on chemotherapy has been added, and the section on pathology has been enlarged. The appendix on splints and plaster has also been revised. The book is well published and should be in all collections on the subject.

Doctors Differ. Five Studies in Contrast: John Elliotson, Hugh O. Thomas, James Mackenzie, William Macewen, and R. W. Philip. By Harley Williams. 12°, cloth, 239 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.50.

The author presents a series of biographies of physicians and surgeons, eminent in their particular fields, and discusses their contrasting personalities. John Elliotson and Anton Mesmer were pioneers in mesmerism. Hugh Owen Thomas, the bone-setter, and his nephew, Sir Robert Jones, were pioneers in orthopedics. Sir James Mackenzie, the well known heart specialist, and Sir William Osler, the clinician, are brought into contrast. Brain surgery is exemplified by Sir William Macewen and Sir Victor Horsley. Sketches of Edward L. Trudeau, of Saranac Lake, New York, famed for his open-air treatment of pulmonary tuberculosis, and Sir Robert Philip, who was a pioneer in the control of the same disease, conclude the book. The text is written in a nontechnical, easy style. The book should prove useful to all persons interested in the history of medicine.

Medical Photography: Radiographic and clinical. By T. A. Longmore, Hon. F.S.R., principal, Kodak School of Medical Radiography and Clinical Photography, honorary editor of *Radiography* and member of Council, Education Committee and Board of Examiners of the Society of Radiographers. With a foreword by Brigadier D. B. McGrigor, O.B.E., M.B., Ch.B., D.M.R.E., Hon. F.S.R., consulting radiologist, The War Office, and president, British Institute of Radiology 1939–42. Fourth edition. 12°, cloth, 1008 pp., with 119 illustrations and 120 plates. New York: Focal Press, 1949. 50/-net.

This fourth edition of a book designed as a textbook for students and beginners has been enlarged to cover all practical aspects of the subject, both technical and clinical. A glossary of terms is appended to the text. There is a selective bibliography and a good index. The printing was done in Great Britain. The book should be in all collections on the subject.

Die Bluteiweisskörper des Menschen: Untersuchungsmethoden und deren klinisch-praktische Bedeutung. By Prof. Dr. med. Ferdinand Wuhrmann, medical physician in chief, Kantonsspital Winterthur, Zürich, and lecturer in internal medicine, University of Zürich; and Dr. Ing. Chem. Charlie Wunderly, scientific principal assistant, Medical University clinic of Zürich. Second edition. 8°, cloth, 387 pp., with 145 illustrations and 4 plates. Basel: Benno Schwabe and Company, 1952. Gebunden Fr. 42.

The first edition of this special work on the white blood corpuscle and its practical clinical importance was published in 1947. It was translated into Spanish in 1949. This new edition has been completely revised and brought up to date. The pertinent literature has been reviewed, and the many references are carried as footnotes to the proper pages. There are extensive indexes of authors and subjects. The publishing is excellent. The book should be in all collections on the blood.

Grundlagen und Sprache der Phthise- und Tuberkuloseforschung. By Professor Dr. Siegfried Gräff, supervising chief physician, Pathologischen Institut des allgem. Krankenhauses Barmbeck, Hamburg. 8°, paper, 61 pp. Stuttgart: Georg Thieme, 1952. Kart. DM 6.60. (Distributed by Grune and Stratton, New York.)

This monograph presents the general aspects of tuberculosis research from the heterologic and morphologic aspects with an analysis of the pertinent literature. There are 78 references to articles carried as footnotes to the pertinent pages. The pamphlet should be in tuberculosis collections.

Practical Procedures. Edited by Sir Heneage Ogilvie, K.B.E., D.M.,M.Ch., F.R.C.S., and William A. R. Thomson, M.D. Second edition. 8°, cloth, 380 pp., with 99 illustrations and 7 tables. London: Eyre and Spottiswoode, 1952. 25s. net. (*The Practitioner Handbooks.*)

The first edition of this manual was published in 1938 and was received so favorably that three reprintings had been made by 1941, when war conditions drove it off the market. The purpose of the book is to furnish information on procedures commonly met with in general practice. Twenty-seven subjects are covered, each written by specialists in their partjcular fields. This so-called second edition is practically a new book. The text has been thoroughly revised and reset. Ten new subjects have been added on the administration of penicillin and streptomycin, hormone implantation therapy, procedures in gynecology and ophthalmology, examination of throat and larynx, biopsy, gastric secretion, immunization and vaccination, enemas, and examination of the rectum. There is a good index and the publishing is excellent. This practical book should prove of value to the practicing physician.

Clot Retraction. By O. E. Budtz-Olsen, M.D., Wernher and Beit Laboratories, University of Cape Town. 8°, cloth, 149 pp., with 40 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $5.50.

This monograph presents a survey of the known literature on clot retraction. There is a bibliography of sixteen pages dating as far back as Thackrah (1819). The text is divided into two parts: a discussion of the subject in detail; and experimental data, comprising thirty-seven experiments. The lack of an index is noted. The printing was done in Holland. The book should be in all collections on the blood.

Mind, Perception and Science. By W. Russell Brain, D.M., F.R.C.P., president of the Royal College of Physicians of London. 12°, cloth, 90 pp. Springfield, Illinois: Charles C Thomas, 1952. $2.50.

The author discusses the problem of perception in its neurologic and philosophic aspects. The material is based largely on lectures and broadcasts delivered during the past five years. The first three chapters are concerned with neurologic questions, and the last four with their philosophic im-

plications. Dr. Brain believes in the autonomy of the mind in its own sphere and discusses this proposition in this monograph.

Surgery and the Endocrine System: Physiologic response to surgical trauma: — operative management of endocrine dysfunction. By James D. Hardy, M.D., assistant professor of surgery, University of Tennessee College of Medicine. 8°, cloth, 153 pp., with 43 illustrations. Philadelphia: W. B. Saunders Company, 1952. $5.00.

In this monograph Dr. Hardy has surveyed the present status of the relation of the endocrine system to surgery and the management of surgery of the endocrine organs. The text is divided roughly into two sections: general considerations, including the alarm reaction in the surgical patient, the metabolic aspects of body-fluid regulation and of shock, the dynamics of nutrition and the relation of nutrition to an adequate response to trauma; and the physiologic basis of early ambulation and notes on convalescence, the endocrinology of surgical infections, thermal burns, tissue repair and neoplasia, and endocrine therapy in surgical patients. A special part discusses the thyroid gland, hyperparathyroidism, functioning tumors of the islands of Langerhans, including hyperinsulinism, the adrenal glands, including pheochromocytoma, the pituitary body, thymus and gonads, and the surgery of these various endocrine organs. The important literature has been surveyed, and bibliographies are appended to the various chapters. The publishing is excellent, and the monograph should be in all medical libraries and in the libraries of endocrinologists and surgeons.

Diabetes and Pregnancy. By Ralph A. Reis, M.D., professor of obstetrics and gynecology, Northwestern University Medical School, and senior attending obstetrician and gynecologist, Michael Reese Hospital; Edwin J. DeCosta, M.D., assistant professor of obstetrics and gynecology, Northwestern University Medical School, and associate attending obstetrician and gynecologist, Michael Reese Hospital; and M. David Allweiss, M.D., associate in medicine, Northwestern University Medical School, and associate attending physician, Department of Medicine, Michael Reese Hospital, Chicago. 8°, cloth, 78 pp. Springfield, Illinois: Charles C Thomas, 1952. $2.50. (Publication No. 158, *American Lecture Series.*)

The text of this monograph is based on the personal experience of the 3 specialists of the Michael Reese Hospital, supplemented by a survey of the literature on the subject. The various aspects of the effects of pregnancy on diabetes and of diabetes on pregnancy are discussed. There is a special chapter on the newborn infant of the diabetic mother. There is a bibliography of 78 titles.

Surgical Gynecology, Including Important Obstetric Operations: A handbook of operative surgery. By J. P. Greenhill, M.D., professor of gynecology, Cook County Graduate School of Medicine, attending gynecologist, Cook County Hospital, and attending obstetrician and gynecologist, Michael Reese Hospital. 8°, cloth, 350 pp., with 98 illustrations by Angela Bartenbach. Chicago, Illinois: Year Book Publishers, Incorporated, 1952. $8.50.

The handbook has been prepared for young gynecologists and general surgeons. The material is arranged by anatomic structures: vulva and perineum, vagina and abdomen. The first chapter discusses preoperative preparation and postoperative care and complications. Practically three fourths of the book is essentially an atlas of 101 diagrammatic plates with appropriate text, illustrating step by step the various operations. There is a good index, and the publishing is good.

Foundation of Neuropsychiatry. By Stanley Cobb, M.D., Bullard Professor of Neuropathology, Harvard Medical School, and psychiatrist-in-chief, Massachusetts General Hospital. (Fifth revised and enlarged edition of the work, formerly known as *A Preface to Nervous Disease.*) 8°, cloth, 287 pp. Baltimore: Williams and Wilkins, 1952.

Dr. Cobb has thoroughly revised this new edition of a fundamental reference work, first published in 1936. A chapter on general neurophysiology and a section dealing with emotional reactions in relation to the autonomic nervous system have been added. All the chapters, except that on the cerebrospinal fluid, have been considerably revised. Short lists of selected references are appended to the various chapters, and there is a good index. The book is recommended for all medical libraries.

Klinische Probleme der vegetativen Regulation und der Neuralpathologie. By Professor Dr. Ferdinand Hoff, director of the I. Medizinischen Universitätsklinik, Frankfurt-am-Main. 8°, paper, 43 pp., with 9 illustrations. Stuttgart: Georg Thieme, 1952. Kart. DM 2.70. (Distributed by Grune and Stratton, New York.)

This small pamphlet on the clinical problems of vegetative regulation and neuropathology has been reprinted from the *Deutsche medizinische Wochenschrift* and thus made available to a large number of interested readers. The pertinent literature is surveyed, and there is a bibliography of selected titles.

The Quiet Art: A doctor's anthology. Compiled by Dr. Robert Coope. 12°, cloth, 284 pp., with frontispiece. Edinburgh: E. and S. Livingstone Limited, 1952. (Distributed by Williams and Wilkins.) $3.00.

The author has made a collection of excerpts from the writings of physicians and others relating to the "quiet art" of medicine, so called by Vergil in the Aeneid, dating from Plato and Hippocrates to Oliver Wendell Holmes and Sir William Osler. There is an index of authors, and the small book is well published. It is recommended for all medical and public libraries.

Ear, Nose and Throat Diseases for the General Practitioner. By William McKenzie, M.B., B.Chir. (Cantab.), F.R.C.S. (Eng.), surgeon, Royal National Throat, Nose and Ear Hospital, and surgeon, Ear, Nose and Throat Department, Prince of Wales Hospital, Tottenham. 12°, cloth, 136 pp., with 9 illustrations. Edinburgh and London: E. and S. Livingstone, Limited, 1952. (Distributed in the United States by Williams and Wilkins.) $2.00.

This small manual is well written, and the material is well arranged. Emphasis is placed on the commoner diseases met with in general practice. The chapter on deafness and hearing aids, including tests, should prove especially useful. There is a good index, and the publishing is excellent.

Dynamic Psychiatry: Transvestism-desire for crippled women. Volume 2. By Louis S. London, M.D. 8°, cloth, 129 pp., with 50 illustrations. New York, New York: Corinthian Publications, Incorporated, 1952. $2.50.

Dr. London presents a unique case of transvestism in which the patient showed a psychopathologic interest in crippled women, dwarfs, freaks and cross-eyed, bearded women, and at times masqueraded as a male or female cripple. During his analysis the patient presented 80 good drawings, 50 of which are reproduced at his request in the belief that similar cases must exist. Dr. London has been unable to discover any in the literature on the subject. The text comprises three parts: anthropologic and historical, from the time of the Emperor Nero to the present; fifty psychobiographic fantasies drawn by the patient, with his own descriptions; and analysis of the case in its various aspects. The small book belongs in all collections on sexual deviations.

An Atlas of General Affections of the Skeleton. By Sir Thomas Fairbank, D.S.O., O.B.E., M.S., Hon.M.Ch. (Orth.), F.R.C.S., consulting orthopedic surgeon and emeritus lecturer in orthopedic surgery, King's College Hospital, consulting surgeon, Hospital for Sick Children, Great Ormond Street, emeritus consulting surgeon, Lord Mayor Treloar Orthopaedic Hospital, Alton, and honorary consultant (orthopedic) to the Army. 4°, cloth, 411 pp., with 509 illustrations. Baltimore: Williams and Wilkins Company, 1951. $10.00.

The author presents 184 case reports of various diseases of the locomotor system and discusses them in detail. Each of

the cases is illustrated by reproductions of radiographs. The extensive literature has been surveyed, and short lists of references are appended to the various cases. There are indexes of authors and subjects. The book should be in all collections on the subject.

Blood Transfusion in Clinical Medicine. By P. L. Mollison, M.D., M.R.C.P., M.R.C.S., director, Medical Research Council's Blood Transfusion Research Unit, and lecturer in the Department of Medicine, Post-graduate Medical School of London. With a foreword by Sir Alan N. Drury, C.B.E., F.R.S. 8°, cloth, 456 pp., with 59 illustrations. Springfield, Illinois: Charles C Thomas, 1952. $8.00.

This special book covers the whole field of blood groups, grouping and transfusion, in their clinical and biologic aspects. There are special chapters on anemia and the hemolytic diseases of the newborn. There is an extensive bibliography and a good index, and the book is well published. The printing was done in Holland. The book should be in all collections on the subject.

The Diagnosis of Nervous Diseases. By the late James Purves-Stewart, K.C.M.G., C.B., M.D. Edin., F.R.C.P., consulting physician to Westminster Hospital, to the West End Hospital for Nervous Diseases and to the Royal National Orthopaedic Hospital; and C. Worster-Drought, M.A., M.D. Cantab., F.R.C.P., physician to the West End Hospital for Nervous Diseases, physician-neurologist to the Metropolitan Hospital, the Royal Cancer Hospital and Bethlem Royal Hospital. Tenth edition. 8°, cloth, 962 pp., with 388 illustrations. Baltimore: Williams and Wilkins Company, 1952. $10.00.

This well known standard book, first published in 1906 by Dr. Purves-Stewart, is now continued by Dr. Worster-Drought, in a tenth edition, speaking well for its soundness and popularity. The text has been thoroughly revised and brought up to date. Many of the chapters and sections have been completely rewritten. The book is well published. The printing was done in Great Britain.

When Doctors Are Patients. Edited by Max Pinner, M.D., and Benjamin F. Miller. 8°, cloth, 364 pp. New York: W. W. Norton and Company, Incorporated, 1952. $3.95.

This volume contains a series of case studies by physicians afflicted with various conditions ranging from heart disease to aging. The material is divided into eight categories. These thirty-three short autobiographies portray adjustment to disease by doctors themselves. The book is well published, and there is a good index. It is recommended for medical history collections.

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, February 10, at 8 p.m. with Professor J. Howard Mueller presiding. The Department of Bacteriology and Immunology of Harvard Medical School will present the following program:

Involvement of Histidine Peptides in the Production of Tetanus Toxin. J. Howard Mueller, Pauline Miller and Harry Gooder.

Histidine Assimilation and Dissimilation in a Histidineless Mutant of *Aerobacter aerogenes*. Boris Magasanik and Doris Karibian.

Virus Growth and Cellular-Energy Production. Monroe D. Eaton and Joan B. Daniels.

The Site of Antibody Formation. Albert H. Coons, Elizabeth H. Leduc and Jeanne M. Connolly.

Mechanism of Acquired Resistance in Tuberculosis: Role of the phagocyte. Emanuel Suter and Barbara Chalfant.

MASSACHUSETTS SCHOOL PHYSICIANS' ASSOCIATION

A meeting of the Massachusetts School Physicians' Association will be held in Margaret Jewett Hall, Mount Auburn Hospital, Cambridge, on Wednesday, March 4, at 8 p.m.

Action will be taken on the recommendation of the special committee appointed last fall "that the minimum salary of school physicians be based on $10 per hour as a minimum."

Plans for the clinical meeting, to be held in May, will be discussed.

ALUMNI POSTGRADUATE CONVENTION COLLEGE OF MEDICAL EVANGELISTS

The Alumni Association, School of Medicine of the College of Medical Evangelists, presents its seventeenth annual Alumni Postgraduate Convention in the Ambassador Hotel, Los Angeles, March 8–10. A program of lectures, panels, motion pictures and scientific and technical exhibits is planned to present to the busy physician new and improved methods of diagnosis and treatment, as well as latest developments in medical science.

The American Academy of General Practice has granted Academy members informal postgraduate credit for attendance at this Assembly.

Informal luncheon round-table discussions will be held in the French Room of the Ambassador Hotel on Sunday and Tuesday, presided over by featured speakers.

REPLACEMENT PROGRAM FOR CERTAIN CATEGORIES OF PHYSICIANS

A program has recently been initiated by the Council on National Emergency Medical Service of the American Medical Association and the three Surgeons General of the armed forces to supply the names of potential replacements for physicians now deferred from military service who are in Priority I or II, or who are thirty-five years of age and under in Priority III.

Medical officers who are scheduled to be released from active duty in the near future and who indicate a desire to work or train in the state of Massachusetts upon their discharge, will be reported periodically (depending on number being released) by the Massachusetts Advisory Committee. These lists will be distributed to Massachusetts hospitals, medical schools, departments of public health and mental health and the Harvard School of Public Health.

It is hoped that this program will be successful in serving as a source of physicians for hospitals and schools, and that it will be of assistance to medical officers in their return to civilian practice.

SOCIETY MEETINGS AND CONFERENCES

February 6. New England Society of Anesthesiologists. Page 827, issue of November 20.

February 6. American College of Radiology. Page 1001, issue of December 18.

February 6–28. Springfield Hospital Educational Program. Page 164, issue of January 22.

February 6–March 27. Combined Anesthesia Teaching Conferences of Boston. Page 210, issue of January 29.

February 7. Treatment of Coronary-Artery Disease: Present status of anticoagulants and early ambulation. Drs. Paul D. White and Samuel A. Levine. Mount Auburn Hospital, Cambridge.

February 9. New England Cardiovascular Society. Page 210, issue of January 29.

February 9–March 23. Postgraduate Course in General Medicine. Cushing Veterans Administration Hospital, Framingham. Page 697, issue of October 30.

February 9 and 10. Annual Congress on Medical Education and Licensure. Page 786, issue of November 13.

February 10. Harvard Medical Society. Notice above.

February 10. Springfield Academy of Medicine. Page 164, issue of January 22.

February 10. New York Society for Circulatory Diseases. Page 210, issue of January 29.

February 11–April 8. Postgraduate Medical Institute. Boston. Page 452, issue of September 18.

February 12. Pentucket Association of Physicians. Pentucket Club, Haverhill.

February 16–April 20. Hartford Medical Society. Page 42, issue of January 1.

February 17. South End Medical Club. Page 164, issue of January 22.

February 18–April 1. Postgraduate Medical Institute Course in General Medicine. Burbank Hospital, Fitchburg. Page 1049, issue of December 25.

February 20. New England Center Hospital House Officers' Association. Page 124, issue of January 15.

(Notices concluded on page xv)